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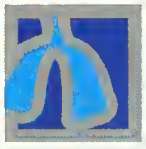

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Editorials, Commentaries, and Reviews To Note

Helping City Children Control Asthma (Medical News & Perspectives)—C Marwick. JAMA 1997;277(19): 1503-1504.

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Enhancing Peer Review of Scientific Manuscripts (Editorial)—RJ Goldberg, JE Dalen. Arch Intern Med 1997;157:380-382.

Prone Positioning and Low-Volume Pressure-Limited Ventilation Improve Survival in Patients with Severe ARDS—R Stocker, T Neff, S Stein, E Ecknauer, O Trentz, E Russi. Chest 1997;111(4):1008.

OBJECTIVES: Investigating the effect of low-volume pressure-limited ventilation and repeated prone positioning on the short-term course and outcome in patients with severe ARDS. SETTING: Level 1 trauma center of a university hospital. PATIENTS: Twenty-five patients suffering from ARDS with a lung-injury score (LIS) ≥ 22.5 admitted consecutively to our ICU from January 1992 to December 1994. METHODS: Mechanical ventilation with peak inspiratory pressure limitation to 35 mbar, irrespective of hypercapnia and prone positioning to achieve adequate oxygenation. SCORING & MEASUREMENTS: Patient assessment with LIS, APACHE (acute physiology and chronic health evaluation) II score, injury severity score, and multiple organ failure score. Blood gas analyses and estimation of static compliance were repeated at least every 4 hours during the treatment period. P_{aO_2}/F_{IO_2} (fraction of inspired oxygen) ratio, alveolo-arterial oxygen difference, and intrapulmonary shunt were calculated according to standard equations. The best values taken from each 4-hour period during the investigation were used to evaluate the best possible performance of the lung within this interval and to investigate the entire course. RESULTS: Mean predicted mortality based on the APACHE II score was 35.4 ± 15.2%. Three of the 25 patients (12%) died. However, none was related to respiratory failure. No pneumothorax occurred. Sixteen patients, lacking any contraindication for prone positioning, responded positively to this change in position, each to a different individual degree. CONCLUSION: We assume that our low mortality in patients with severe ARDS might be due mainly to low-volume pressure-limited ventilation and prone positioning. This simple strategy seems to allow successful treatment for patients with severe ARDS.

A Community-Based Regional Ventilator Weaning Unit: Development and Outcomes—PH Bagley, E Cooney. Chest 1997;111(4):1024.

OBJECTIVE: Description of the development of a community-based weaning unit and the outcomes from that unit. DESIGN: Review of admissions, classified by etiology of ventilator dependence, with attention to disposition, length of stay, and time to wean. SETTING: Long-term acute-care facility in Worcester, Mass. PATIENTS: Two hundred seventy-eight ventilator-dependent patients admitted to a ventilator unit from 1988 through May 1995. Admissions criteria did not include prognostic considerations. INTERVENTIONS: Selected patients were entered into a formal weaning program beginning in 1992. MEASUREMENTS: Through the study period, there was a substantial growth in annual admissions, primarily due to increases in patients surviving a catastrophic acute illness. Overall, 107 of 278 (38%) patients were liberated from mechanical ventilation for at least 7 consecutive days and nights. Of the patients admitted 1993 to 1995, 31% died, 20% were discharged to a long-term care facility, 29% returned home, and 18% either remained as residents of the unit or had been transferred to acute-care facilities and were unavailable for follow-up. The highest weaning success was seen in patients with ventilator dependence from postoperative causes (58%) and acute lung injury (57%); the least success was seen in patients with ventilator dependence from COPD and neuromuscular diseases (22% each). The average time from admission to weaning fell within each diagnostic category throughout the study period. CONCLUSIONS: Rehabilitation-based ventilator weaning units play an important role in the spectrum of medical care necessary in population centers. Excellent results can result from community-based units with open admissions policies.

Performance Characteristics of Bilevel Pressure Ventilators: A Lung Model Study—T Bunburaphong, H Imanaka, M Nishimura, D Hess, RM Kacmarek. Chest 1997;111(4): 1050.

Bi-level pressure ventilators are being used increasingly to provide noninvasive ventilator support in the management of obstructive sleep apnea, chronic ventilatory failure, and acute respiratory failure. However, the ability of these ventilators to respond to inspiratory demand without imposing expiratory loads has not been evaluated extensively. We evaluated the performance of 9 bi-level pressure ventilators in a lung model, as compared with the Nellcor Puritan-Bennett 7200ae adult critical care ventilator. All ventilators were set to provide pressure support ventilation (PSV) and positive end-expiratory pressure (PEEP) at a rate of 10 breaths/min with an inspiratory time of 1.0 second. Simulated pleural pressure, airway pressure, and flow at airway opening were continuously monitored. We studied the effects of 3 PSV levels (5, 10, and 15 cm H_2O) with 5 cm H_2O PEEP at 2 lung compliances (50 and 80 mL/cm H_2O) and 4 peak inspiratory flow demands (20, 40, 60, and 80 L/min) on 7 dependent variables: inspiratory delay time (D-I), inspiratory trigger pressure (P-I), inspiratory area percent (Area I %), expiratory delay time (D-E), supraplateau expiratory pressure change (P-E), expiratory area (Area E), and ventilator peak flow (VPF). Most ventilators performed as well as or significantly ($p < 0.05$) better than the 7200ae in all studied variables. Compliance did not significantly affect ventilator performance. Increasing inspiratory flow

demand significantly ($p < 0.05$) increased D-I, P-I, P-E, and VPF and decreased Area I % with most ventilators. As ventilatory demand increased, D-E and Area E significantly ($p < 0.05$) changed. With some units, D-E and Area E increased, while with others they decreased. Most bi-level pressure ventilators evaluated were able to respond to high ventilatory demands and outperformed the Nellcor Puritan-Bennett 7200ae ventilator.

The Components of a Respiratory Rehabilitation Program: A Systematic Overview—Y Lacasse, GH Guyatt, RS Goldstein. Chest 1997; 111(4):1077.

OBJECTIVE: To determine the contribution of the various components of a rehabilitation program to the improvement of exercise capacity and health-related quality of life (HRQL) in patients with COPD. DATA SOURCES: MEDLINE (1966 to April 1996) was searched. Abstracts presented at international conferences were also hand searched for additional relevant trials. Bibliographies of the retrieved articles were reviewed. Experts in rehabilitation were consulted to uncover unpublished trials. STUDY SELECTION: Randomized controlled trials (RCTs) of exercise training, breathing exercises, education, and psychosocial support in patients with COPD were primarily included if (1) the treatment effect of a specific component of a rehabilitation program could be isolated, and (2) exercise capacity, HRQL, compliance with medical therapy, and/or knowledge about the disease were measured. DATA SYNTHESIS: A best-evidence synthesis was conducted; 22 RCTs contributed to the analysis. We found the following: (1) the patients exposed to interventions that included exercise training improved their functional exercise capacity and HRQL; (2) exercise training was muscle specific; (3) the evidence to support inspiratory muscle training and other breathing exercises as an adjunct to exercise training in COPD remains equivocal; (4) the contribution of education has not been well addressed; and (5) psychosocial support reduced dyspnea acutely and, when used as an adjunct to rehabilitation, promoted compliance with an exercise regimen and improved HRQL. CONCLUSION: Respiratory rehabilitation is likely to improve functional exercise capacity and HRQL if it includes exercise training and psychosocial support. Further research is required to better define the types and intensity of exercise as well as the influence of respiratory muscle training and patient education.

Certified First Responder: A Comprehensive Model for Pediatric Training—D Markenson, G Foltin, M Tunik, A Cooper, M Treiber, C Welborn, et al. Pediatr Emerg Care 1997;13(2):134.

The purpose of this document is to present a general approach to educating the First Responder in Emergency Pediatric Care. The First Responder is especially important in the emergency care of the sick or injured child. The majority of mortality and morbidity associated with pediatric emergencies is a result of airway and ventilatory compromise. In addition, most airway and ventilation problems can be corrected with only basic life support interventions that are within the scope of practice of the First Responder. As a result, it is of paramount importance to assure that the First Responder is adequately trained in the initial care of the pediatric patient. This document will review some of the key objectives and topics which the First Responder needs to understand in order to adequately care for children until further emergency care arrives. Templates for lesson plans and suggested activities for training the First Responder are also presented.

Hyperpnea-Induced Changes in Parenchymal Lung Mechanics in Normal Subjects and in Asthmatics—DA Kaminsky, SE Wenzel, C Carcano, D Gurka, D Feldsien, CG Irvin. Am J Respir Crit Care Med 1997;155:1260.

The effects of hyperpnea on parenchymal lung mechanics are unknown, but they may contribute to the resultant airflow limitation commonly seen in asthma. To investigate these effects, we measured the following parameters in 7 asthmatic and 6 normal subjects before and after 5 minutes of hyperpnea: specific conductance, upstream resistance, static compliance, the coefficient of retraction, lung volumes, lung hysteresis, and the ratio of maximal to partial flow rates (the M:P ratio, an indicator of the effect of deep inhalation on airflow, and a measure of relative airway and parenchymal hysteresis). In addition to a central effect on the airways, as shown by significant falls in specific conductance, hyperpnea in asthmatics, but not in normal subjects, resulted in significant increases in residual volume and pressure-volume hysteresis, suggestive of changes in parenchymal lung mechanics. The M:P ratio also increased in the asthmatics, consistent with greater increases in airway than in parenchymal hysteresis after hyperpnea. We conclude that hyperpnea has significant effects on the lung parenchyma that contribute to airflow limitation in asthmatics, and we hypothesize that these effects may be due to alterations in peripheral airway smooth muscle tone and surfactant function.

Failure of Aggressive Therapy To Alter Outcome in Pediatric Near-Drowning—L Spack, R Gedeit, M Splaingard, PL Havens. Pediatr Emerg Care 1997;13(2):98.

OBJECTIVES: To identify predictors of outcome in pediatric near-drowning victims, and to measure the effectiveness of therapy in pediatric near-drowning victims by assessing clinical outcome as a function of injury severity at presentation and therapeutic interventions during hospitalization. DESIGN: Retrospective chart review at a tertiary care university associated Children's Hospital from January 1976 to July 1992. MEASUREMENTS & MAIN RESULTS: Initial intensive care unit (ICU) assessment included a Glasgow Coma Score (GCS) and a Pediatric Risk of Mortality (PRISM) Score. Outcome was assessed using a standard scoring system classifying functional abilities at hospital discharge as no functional disability, independent, partially independent, or total dependence on caregivers for function. Forty (49%) of 81 died. Of the survivors, 26 (63%) had no functional disability or were partially dependent at hospital discharge. Of the 47 (64%) patients with a GCS ≤ 4 on presentation to the ICU, 37 (79%) died and 10 (21%) were dependent in all areas of function at discharge. Of the 40 (60%) patients who had a PRISM score < 20, 98% either died or were completely dependent at discharge. Of the 49 patients who were asystolic upon arrival to the emergency department (ED), 76% died, and the rest were completely dependent. Logistic regression showed that therapy had no independent effect on outcome when disease severity was accounted for. CONCLUSIONS: Severity of illness measured by GCS and PRISM score in the ICU can be useful in predicting outcome. For patients cared for in a Pediatric Intensive Care Unit, those with asystole on arrival at the ED had uniformly poor outcome. Currently available therapies do not alter outcome.

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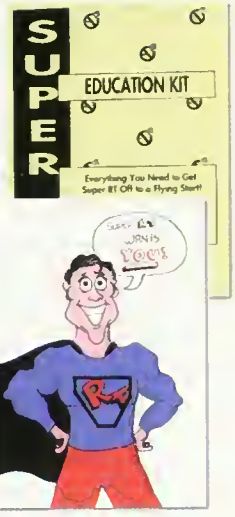

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MEDICAL SOCIETIES SUPPORT AARC CONGRESS - Sam Giordano, AARC Executive Director, announced that, as of the writing of this ***Update***, the following medical associations are supporting the AARC's ***43rd International Respiratory Congress***: American Association of Critical-Care Nurses; American College of Allergy, Asthma and Immunology; American Society of Electroneurodiagnostics Technologists: American Society of Testing and Materials; Association of Polysomnographic Technologists; Clinical Laboratory Management Association; Respiratory Nursing Society; and Visiting Nursing Association of America. In accepting this support, Mr. Giordano said, "The AARC is recognizing the trend for multiskilled practitioners and a need to share our ***Congress*** with all who are involved in the management of respiratory diseases." As part of this support, the organizations will promote the ***Congress*** to their members. The AARC will also mail the official ***Congress*** program to the members of these organizations. The final result, Mr. Giordano added, "should be the best-attended AARC meeting ever."

SCRUSHY TO GIVE KEYNOTE ADDRESS - Richard Scrushy, chairman and CEO of HealthSouth, will deliver the Keynote Address at the ***43rd International Respiratory Congress***. Mr. Scrushy heads the nation's leading provider of outpatient surgery and rehabilitation services. A former respiratory therapist, Mr. Scrushy is a key person in today's health care and a man who uses a lot of numbers when he talks ... like 1,000 patient care locations in 50 states and 130 million people covered under some type of managed care agreement. The Keynote Address is scheduled as part of the Opening Session, Saturday morning, December 6.

FOUNDATION TO CONDUCT SILENT AUCTION - At this year's ***Congress,*** the American Respiratory Care Foundation (ARCF) is adding something new! In an effort to increase the amount of funds available for research projects and other philanthropic programs, the ARCF is planning its first-ever *Silent Auction*. The *Auction* will offer attendees a good time and the chance to pick up bargains on personal electronics, respiratory equipment, entertainment packages, and more. Items will be on display throughout the meeting, allowing attendees to submit bids at their convenience.

KITTREDGE LECTURER ANNOUNCED - Bill Galvin, AARC Program Committee Chair, announces that Dr. Neil MacIntyre, Professor of Medicine and Medical Director of Respiratory Care Services at Duke University Medical Center, will give the Phil Kittredge Memorial Lecture at this year's ***International Respiratory Congress***. One of the two premier lectures at the ***Congress***, the Kittredge Lecture was established 13 years ago by the Program Committee to provide a critical and incisive evaluation of an aspect of emerging or increasing importance to the profession. Dr. MacIntyre's lecture, "Mechanical Ventilation: The Next 50 Years," is scheduled for Monday, December 8.

HISTORICAL EXHIBIT - The AARC is celebrating its 50th Anniversary in 1997 and we are inviting you to visit our special Historical Exhibit in New Orleans (in the Exhibit Hall during exhibit hours). You don't want to miss the opportunity to experience how our profession evolved into a vital element of today's health care team!

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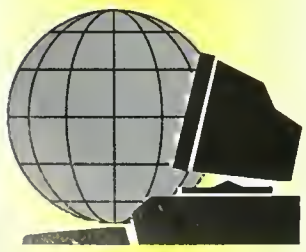

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Interpreting Small Differences in Functional Status: The Six-Minute Walk Test in Chronic Lung Disease Patients—DA Redelmeier, AM Bayoumi, RS Goldstein, GH Guyatt. Am J Respir Crit Care Med 1997;155:1278.

Functional status measurements are often difficult to interpret because small differences may be statistically significant but not clinically significant. How much does the Six-Minute Walk test (6MW) need to differ to signify a noticeable difference in walking ability for patients with chronic obstructive pulmonary disease (COPD)? We studied individuals with stable COPD (n = 112, mean age = 67 yr, mean FEV_1 = 975 mL) and estimated the smallest difference in 6MW distances that was associated with a noticeable difference in patients' subjective comparison ratings of their walking ability. We found that the 6MW was significantly correlated with patients' ratings of their walking ability relative to other patients (r = 0.59, 95% confidence interval [CI]: 0.54 to 0.63). Distances needed to differ by 54 m for the average patient to stop rating themselves as "about the same" and start rating themselves as either "a little bit better" or "a little bit worse" (95% CI: 37 to 71 m). We suggest that differences in functional status can be statistically significant but below the threshold at which patients notice a difference in themselves relative to others; an awareness of the smallest difference in walking distance that is noticeable to patients may help clinicians interpret the effectiveness of symptomatic treatments for COPD.

Adult Patients May Outgrow Their Asthma: A 25-Year Follow-Up Study—CIM Panhuysen, JM Vonk, GH Koëter, JP Schouten, R van Altena, ER Bleecker, DS Postma. Am J Respir Crit Care Med 1997;155:1267.

The present study investigated the outcome of asthma in a population of 181 adult patients 13 to 44 years of age (median, 24 yr) who were extensively tested between 1962 and 1970 and in whom asthma was diagnosed. When retested 25 years later, 38 subjects (21%) did not show bronchial hyperresponsiveness (BHR) (PC_{20} > 16 mg/mL), 45 subjects (25%) showed a FEV_1 > 90% predicted, and 72 subjects (40%) did not report pulmonary symptoms. When absence of asthma was defined as no BHR, FEV_1 > 90% predicted, and the absence of pulmonary symptoms reported by the patient, 20 subjects (11%) were no longer considered asthmatic when retested. Absence of asthma after 25 years was associated with a younger age and less severe airway obstruction at first testing, odds ratios (OR) being 0.36 for age/10 years, and 1.42 for FEV_1/height^2 (dL/m^2). Absence of BHR was associated with a younger age, a higher FEV_1, and a shorter untreated period (years between onset of asthma symptoms and specialized treatment of the disease) at first testing, and a lower total serum IgE level (IU/L) at second testing (OR, 0.48 for age/10 yr; OR, 1.37 for FEV_1/height^2; OR, 0.93 for untreated period; OR, 0.33 for log [IgE]). Neither sex nor atopy (1 or more positive skin tests) were significant determinants of the outcome of both asthma and BHR. Our results suggest that in a substantial proportion of symptomatic asthmatics the disease improved, and that subsets may outgrow their asthma, even in adulthood. The data lend indirect support to the hypothesis that milder disease and earlier intervention are important for a beneficial outcome of asthma.

Bovine Surfactant Therapy for Patients with Acute Respiratory Distress Syndrome—TJ Gregory, KP Steinberg, R Spragg, JE Gadek, TM Hyers, WJ Longmore, et al. Am J Respir Crit Care Med 1997;155:1309.

Lung surfactant is deficient in patients with acute respiratory distress syndrome (ARDS). We performed a randomized, prospective, controlled, open-label clinical study of administration of a bovine surfactant to patients with ARDS to obtain preliminary information about its safety and efficacy. Patients received either surfactant by endotracheal instillation in addition to standard therapy or standard therapy only. Three different groups of patients receiving surfactant were studied: patients receiving up to 8 doses of 50 mg phospholipids/kg, those receiving up to 8 doses of 100 mg phospholipids/kg, and those receiving up to 4 doses of 100 mg phospholipids/kg. Outcome measures included ventilatory support parameters, arterial blood gases, organ system failures, bronchoalveolar lavage (BAL) analyses, immunologic analyses, survival, and adverse events during the 28-day study period. Fifty-nine study patients were evaluable; 43 in the surfactant group and 16 in the control group. The F_{IO_2} at 120 hours after treatment began was significantly decreased only for patients who received up to 4 doses of 100 mg phospholipids/kg surfactant as compared with control patients (p = 0.011). Mortality in the same group of patients was 18.8%, as compared with 43.8% in the control group (p = 0.075). The surfactant instillation was generally well tolerated, and no safety concerns were identified. This pilot study presents preliminary evidence that surfactant might have therapeutic benefit for patients with ARDS, and provides rationale for further clinical study of this agent.

Quality of Life Changes in COPD Patients Treated with Salmeterol—PW Jones, TK Bosh. Am J Respir Crit Care Med 1997;155:1283.

Changes in health-related quality of life (HRQoL) were evaluated in patients with chronic obstructive pulmonary disease (COPD) following treatment with placebo, salmeterol 50 μg twice a day or 100 μg twice a day by metered-dose inhaler. Patients completed the disease-specific St George's Respiratory Questionnaire (SGRQ) and the Medical Outcomes Study Short Form 36 (SF-36) at

baseline and after 16 weeks of treatment. Data from 283 patients (95 patients in the placebo group and 94 in each salmeterol group) were available for HRQoL analysis. Apart from a small difference in ages, all treatment groups were well matched at baseline in terms of forced expiratory volume in 1 second (FEV_1) and HRQoL scores. Compared with placebo, salmeterol 50 μg twice a day was associated with significant improvements in SGRQ "Total" and "Impacts" scores which exceeded the threshold for a clinically significant change. This was not seen with salmeterol 100 μg twice a day. Changes in SGRQ and SF-36 scores correlated. They also showed a weak but significant relationship with FEV_1. This study has shown that a modest change in lung function may be associated with clinically significant gain in health and well-being in COPD patients.

Adverse Drug Events in Hospitalized Patients: Excess Length of Stay, Extra Costs, and Attributable Mortality—DC Classen, SL Pestotnik, RS Evans, JF Lloyd, JP Burke. JAMA 1997; 277(4):301.

OBJECTIVE: To determine the excess length of stay, extra costs, and mortality attributable to adverse drug events (ADEs) in hospitalized patients. DESIGN: Matched case-control study. SETTING: The LDS Hospital, a tertiary care health care institution. PATIENTS: All patients admitted to LDS Hospital from January 1, 1990, to December 31, 1993, were eligible. Cases were defined as patients with ADEs that occurred during hospitalization; controls were selected according to matching variables in a stepwise fashion. METHODS: Controls were matched to cases on primary discharge diagnosis related group (DRG), age, sex, acuity, and year of admission; varying numbers of controls were matched to each case. Matching was successful for 71% of the cases, leading to 1,580 cases and 20,197 controls. MAIN OUTCOME MEASURES: Crude and attributable mortality, crude and attributable length of stay, and cost of hospitalization. RESULTS: ADEs complicated 2.43/100 admissions to the LDS Hospital during the study period. The crude mortality rates for the cases and matched controls were 3.5% and 1.05%, respectively ($p < 0.001$). The mean length of hospital stay significantly differed between the cases and matched controls (7.69 vs 4.46 days; $p < 0.001$) as did the mean cost of hospitalization ($10,010 vs $5,355; $p < 0.001$). The extra length of hospital stay attributable to an ADE was 1.74 days ($p < 0.001$). The excess cost of hospitalization attributable to an ADE was $2,013 ($p < 0.001$). A linear regression analysis for length of stay and cost controlling for all matching variables revealed that the occurrence of an ADE was associated with increased length of stay of 1.91 days and an increased cost of $2,262 ($p < 0.001$). In a similar logistic regression analysis for mortality, the increased risk of death among patients experiencing an ADE was 1.88 (95% confidence interval, 1.54-2.22; $p < 0.001$). CONCLUSION: The attributable lengths of stay and costs of hospitalization for ADEs are substantial. An ADE is associated with a significantly prolonged length of stay, increased economic burden, and an almost 2-fold increased risk of death. *See the related editorial:* ***Putting Adverse Drug Events into Perspective****—J Avorn. JAMA 1997;277(4):341-342.*

The Costs of Adverse Drug Events in Hospitalized Patients—DW Bates, N Spell, DJ Cullen, E Burdick, N Laird, LA Petersen, et al for the Adverse Drug Events Prevention Study Group. JAMA 1997:277(4):307.

OBJECTIVE: To assess the additional resource utilization associated with an adverse drug event (ADE). DESIGN: Nested case-control study within a prospective cohort study. PARTICIPANTS: The cohort included 4,108 admissions to a stratified random sample of 11 medical and surgical units in 2 tertiary-care hospitals over a 6-month period. Cases were patients with an ADE, and the control for each case was the patient on the same unit as the case with the most similar pre-event length of stay. MAIN OUTCOME MEASURES: Post-event length of stay and total costs. METHODS: Incidents were detected by self-report stimulated

LOOK FOR THE RESPIRATORY CARE Special Issue

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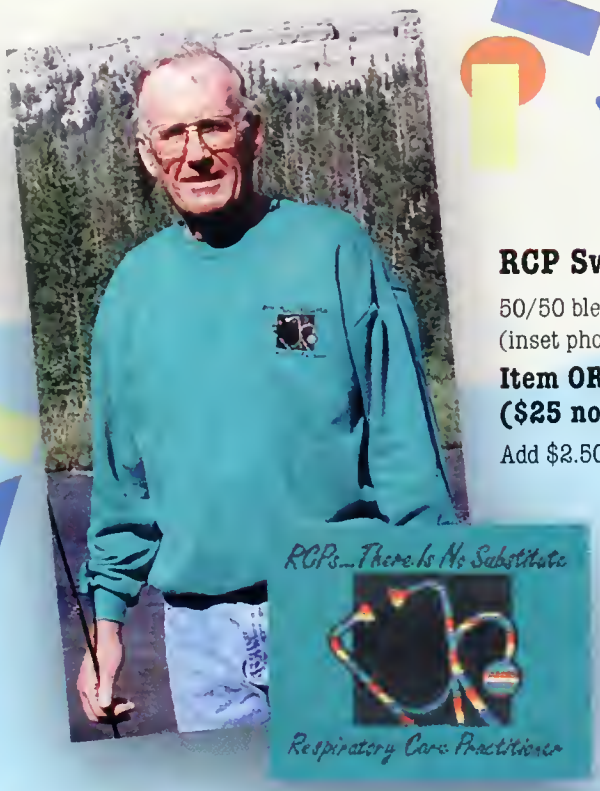

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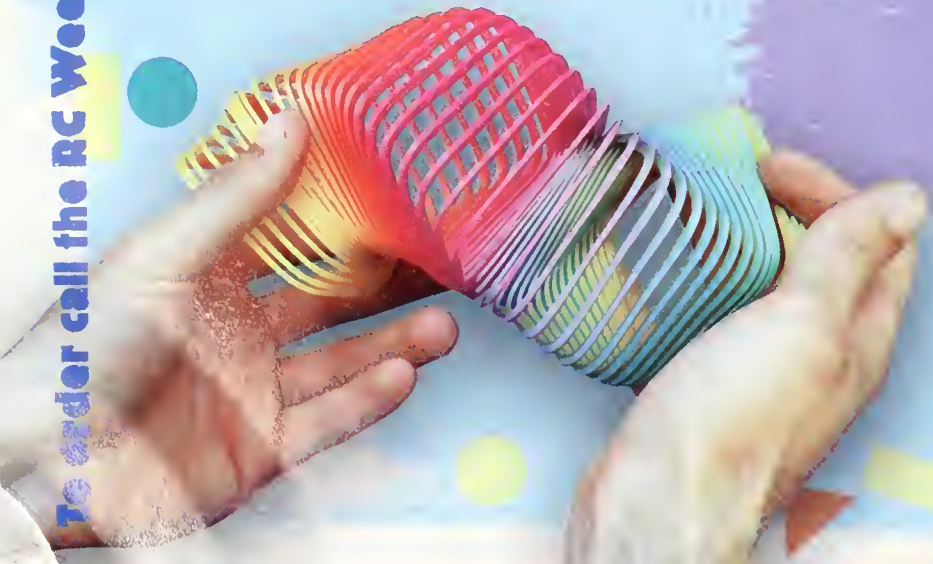

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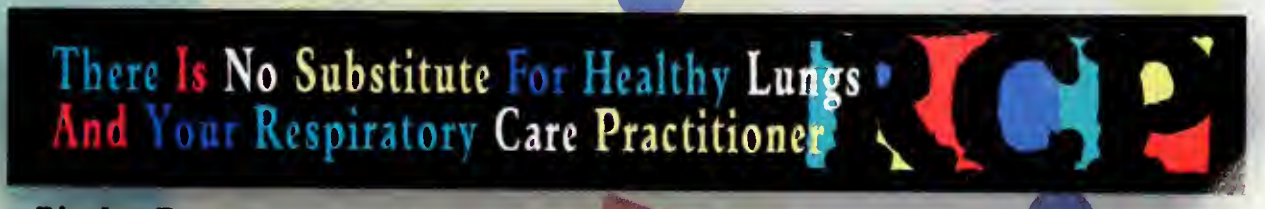

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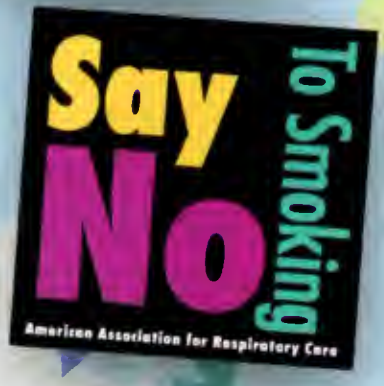

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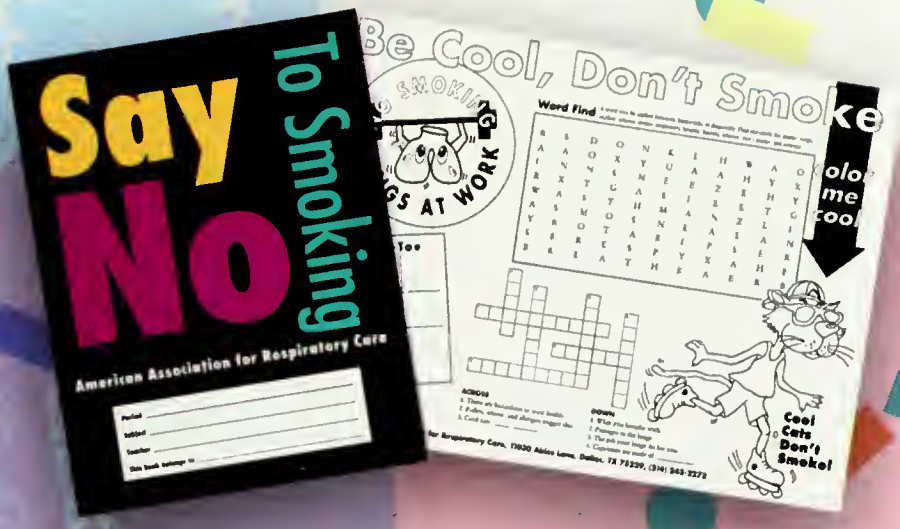

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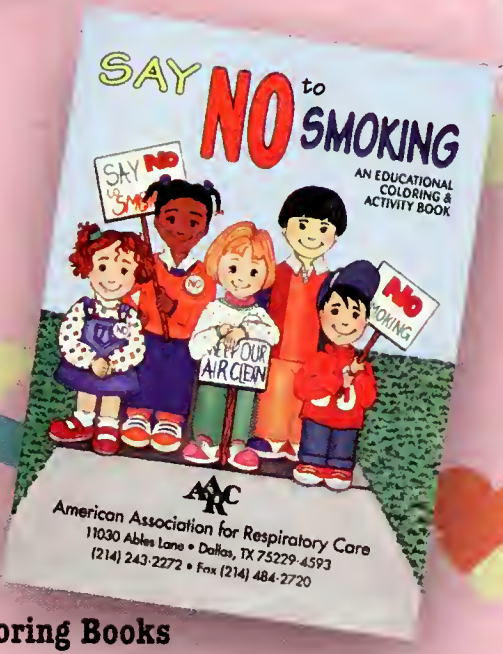
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by nurses and pharmacists and by daily chart review, and were classified as to whether they represented ADEs. Information on length of stay and charges was obtained from billing data, and costs were estimated by multiplying components of charges times hospital-specific ratios of costs to charges. RESULTS: During the study period, there were 247 ADEs among 207 admissions. After outliers and multiple episodes were excluded, there were 190 ADEs, of which 60 were preventable. In paired regression analyses adjusting for multiple factors, including severity, comorbidity, and case mix, the additional length of stay associated with an ADE was 2.2 days ($p = 0.04$), and the increase in cost associated with an ADE was $3,244 ($p = 0.04$). For preventable ADEs, the increases were 4.6 days in length of stay ($p = 0.03$) and $5,857 in total cost ($p = 0.07$). After adjusting for our sampling strategy, the estimated postevent costs attributable to an ADE were $2,595 for all ADEs and $4,685 for preventable ADEs. Based on these costs and data about the incidence of ADEs, we estimate that the annual costs attributable to all ADEs and preventable ADEs for a 700-bed teaching hospital are $5.6 million and $2.8 million, respectively. CONCLUSIONS: The substantial costs of ADEs to hospitals justify investment in efforts to prevent these events. Moreover, these estimates are conservative because they do not include the costs of injuries to patients or malpractice costs. *See the related editorial: **Putting Adverse Drug Events into Perspective**—J Avorn. JAMA 1997;277(4):341-342.*

Factors Related To Errors in Medication Prescribing—TS Lesar, L Briceland, DS Stein. JAMA 1997;277(4):312.

OBJECTIVE: To quantify the type and frequency of identifiable factors associated with medication prescribing errors. DESIGN & SETTING: Systematic evaluation of every third prescribing error detected and averted by pharmacists in a 631-bed tertiary care teaching hospital between July 1,1994, and June 30,1995. Each error was concurrently evaluated for the potential to result in adverse patient consequences. Each error was retrospectively evaluated by a physician and 2 pharmacists and a factor likely related to the error was identified. PARTICIPANTS: All physicians prescribing medications during the study period and all staff pharmacists involved in the routine review of medication orders. MAIN OUTCOME MEASURES: Frequency of association of factors likely related to medication errors in general and specific to medication classes and prescribing services (needed for medical, pediatric, obstetric-gynecologic, surgical, or emergency department patients); and potential consequences of errors for negative patient outcomes. RESULTS: A total of 2,103 errors thought to have potential clinical importance were detected during the 1-year study period. The overall rate of errors was 3.99 errors/1,000 medication orders, and the error rate varied among medication classes and prescribing services. A total of 696 errors met study criteria (ie, errors with the potential for adverse patient effects) and were evaluated for a likely related factor. The most common specific factors associated with errors were decline in renal or hepatic function requiring alteration of drug therapy (97 errors, 13.9%), patient history of allergy to the same medication class (84 errors, 12.1%), using the wrong drug name, dosage form, or abbreviation (total of 79 errors, 11.4%, for both brand name and generic name orders), incorrect dosage calculations (77 errors, 11.1 %), and atypical or unusual and critical dosage frequency considerations (75 errors, 10.8%). The most common groups of factors associated with errors were those related to knowledge and the application of knowledge regarding drug therapy (209 errors, 30%); knowledge and use of knowledge regarding patient factors that affect drug therapy (203 errors, 29.2%); use of calculations, decimal points, or unit and rate expression factors (122 errors, 17.5%); and nomenclature factors (incorrect drug name, dosage form, or abbreviation) (93 errors, 13.4%). CONCLUSIONS: Several easily identified factors are associated with a large proportion of medication prescribing errors. By improving the focus of organizational, technological, and risk management educational and training efforts using the factors commonly associated with prescribing errors, risk to patients from adverse drug events should be reduced. *See the related editorial: **Putting Adverse Drug Events into Perspective**—J Avorn. JAMA 1997;277(4):341-342.*

Aerosol Delivery during Continuous Nebulization—M McPeck, R Tandon, K Hughes, GC Smaldone. Chest 1997;111(5):1200.

BACKGROUND & OBJECTIVES: Continuous administration of aerosolized β_2-agonists has been suggested as an effective treatment for severe reversible airways disease. To facilitate continuous therapy and avoid a feed system for small-volume nebulizers (SVNs), a large-volume medication nebulizer (Vortran HEART) was developed. The goal of this study was to determine actual drug delivery of the HEART and conventional SVNs for both adult and pediatric breathing patterns. DESIGN: Output studies were conducted on comparable samples of CIS-US AeroTech II and Hospitak PowerMist SVNs and Vortran HEART large-volume continuous nebulizers. To duplicate clinical aerosol delivery via an aerosol mask, drug particles were inhaled through the mouth of a model of a human face for 2 test breathing patterns (adult = tidal volume [V_T] of 500 mL, 20 breaths/min, duty cycle of

40%; pediatric = V_T of 100 mL, 35 breaths/min, duty cycle of 40%), generated by a ventilator. Radiolabeled particles of saline solution, confirmed to behave identically to albuterol, were collected on absolute filters at the mouth of the face to measure the actual mass of albuterol particles delivered to the airway opening. RESULTS: The AeroTech II and PowerMist SVNs delivered 5.14 and 3.74 mg/h, respectively, for the adult breathing pattern and 2.97 and 2.48 mg/h, respectively, for the pediatric breathing pattern. Drug delivery rates of the HEART were a function of drug concentration and ranged from 0.87 to 3.48 mg/h for the adult breathing pattern. For the pediatric breathing pattern, drug delivery rate was a function of drug concentration and inspired minute ventilation and ranged from 0.41 to 1.83 mg/h. CONCLUSION: Our data demonstrate that drug delivery to the patient, expressed as inhaled mass over time, is similar for continuous nebulization (HEART system) and intermittently filled SVNs. In addition, for all nebulizers, the influence of the pediatric breathing pattern needs to be considered. Continuous nebulization permits the redistribution of health care personnel and may reduce the costs of therapy. *See the related editorial:* ***Respiratory Drug Delivery****—PJ Anderson. Chest 1997;111(5):1155-1156.*

Measuring Nebulizer Output: Aerosol Production vs Gravimetric Analysis—R Tandon, M McPeck, GC Smaldone. Chest 1997;111 (5):1361.

OBJECTIVES: The function of jet nebulizers has been measured traditionally by gravimetric methods, ie, by weighing nebulizers before and after nebulization. Newer techniques measure aerosol output directly by analyzing aerosolized drug or tracer, ie, radioactive ^{99m}Tc. Because of evaporation, the equivalence of these methods is uncertain. The aim of this study was to determine if the gravimetric method is an accurate measure of aerosol production under different conditions of aerosol generation (ie, nebulizer type, flow rate, pressure, volume fill, and concentration of solution used to nebulize a drug). METHODS: In the first phase of the study, we measured the aerosol output of 9 commercially available jet nebulizers (AvaNeb; Up-Draft-Hudson RCI; Cirrus-Intersurgical Inc; DeVilbiss 646-DeVilbiss; Powermist-Hospitak, Inc; Respirgard II-Marquest Medical Products; Seamless-Seamless/Dart Respiratory; Salter; Salter Labs; Airlife-Baxter Health Care) run under commonly used conditions (2.5 mL volume fill, 2.0 mL normal saline solvent, 0.5 mL albuterol, flow of 6 L/min, and pressures averaging 15.0 ± 2.3 [mean ± SD] pounds per square inch [on the] gauge [psig] provided by a DeVilbiss PulmoAide compressor) with simultaneously measured gravimetrics and filtered radioactivity. Each nebulizer was run to dryness with data acquired every 2 minutes. The change in the weight of the nebulizer and radioactivity captured on the filter were expressed as percentages of the total in the nebulizer solution. In the second phase of the study, the experiments were repeated using the same nebulizers with a volume fill of 5 mL (diluted to half normal saline solution plus albuterol), flow of 10 L/min, and pressures of 35.6 ± 8.8 psig. RESULTS: The cumulative (sum of all 2-min runs) weight loss for each individual nebulizer ranged from 25.00 to 64.55% and cumulative aerosol captured varied from 12.63 to 38.76%. While different, the weight loss and aerosol captured were closely correlated ($y = -0.62 + 0.62x$; $r = 0.961$, $p < 0.0001$). Changing volume fill and concentration of solvent did not affect this correlation ($p = 0.921$ and 0.373, respectively). However, changing flow from 6 L/min to 10 L/min significantly ($p = 0.02$) affected the relationship ($y = -3.80 + 0.83x$; $r = 0.969$, $p < 0.001$). CONCLUSIONS: When compared with direct methods such as filtering generated particles, the gravimetric method of assessing nebulizer function overestimates aerosol output by 1.8 ± 0.18 times, presumably because of the loss of solvent during nebulization. However, the relationship between methods is predictable and appears unaffected by changing the type of nebulizer, volume fill, and concentration of solvent. Changes in nebulizer flow and pressure significantly affected the correlation. Gravimetric methods can be used as simple and convenient screening techniques for comparing jet nebulizers under a wide range of experimental conditions.

Combination of Tracheal Gas Insufflation and Airway Pressure Release Ventilation—K Okamoto, H Kishi, H Choi, T Sato. Chest 1997; 111(5):1366.

OBJECTIVE: We hypothesized that the continuous gas flow administration delivered through an insufflation catheter positioned above the carina during airway pressure release ventilation (APRV) would facilitate carbon dioxide (CO_2) elimination, resulting in normocarbia with a substantially reduced peak airway pressure (P_{aw}). To test this hypothesis, we compared intermittent positive pressure ventilation (IPPV), tracheal gas insufflation (TGI), APRV, and combined TGI and APRV (TGI + APRV). DESIGN: Animal study with random application of 4 ventilatory modes in a canine restrictive-thorax model with and without pulmonary edema. SETTING: Research laboratory at Kumamoto (Japan) University School of Medicine. SUBJECTS: Six mongrel dogs. INTERVENTIONS: Application of 4 ventilatory modes (IPPV, TGI, APRV, and TGI + APRV). MEASUREMENTS & RESULTS: TGI + APRV facilitated CO_2 elimination. The peak P_{aw} was significantly lower during TGI + APRV than during IPPV (nonpulmonary edema model: 15 ± 4 vs 28 ± 9 cm H_2O; $p < 0.05$; pulmonary edema model: 20 ± 4 vs 34 ± 10 cm H_2O; $p < 0.05$). Normocarbia was observed in both models. Neither TGI nor APRV alone maintained normocarbia. CONCLUSION: The combined use of TGI and APRV is a more effective method of maintaining normocarbia with reduced peak P_{aw} than either IPPV or APRV alone.

Comparison of Pressure Support Ventilation and Assist-Control Ventilation in the Treatment of Respiratory Failure—M Tejeda, JH Boix, F Álvarez, R Balanzá, M Morales. Chest 1997;111(5):1322.

OBJECTIVE: To assess whether pressure support ventilation (PSV) could be used as an alternative ventilatory mode to assist-control (A/C) ventilation in the treatment of respiratory failure. DESIGN: A short-term (4-h) prospective study in which the beneficial effect of PSV on respiratory mechanics, gas exchange, arterial oxygenation, cardiovascular hemodynamics, and oxygen consumption was compared with A/C ventilation. SETTING: ICU of a community hospital. PATIENTS: Forty-five patients (mean age, 62.8 [11.8] years) with respiratory failure secondary to COPD, restrictive disorders, or neuromuscular disease requiring mechanical ventilatory support in the ICU were selected for study. INTERVENTIONS: The mean duration of mechanical ventilation before the study was 7.16 (8.64) days. Patients were switched to the PSV mode of the mechanical ventilator for a period of 4 hours after which conventional A/C ventilation was resumed. RESULTS: Patients supported with PSV compared with A/C ventilation showed significantly higher tidal volume, minute ventilation, and inspiratory time in association with significantly lower pressure in the airway and I:E ratio. With regard to gas exchange data, an increase in dead space/tidal volume ratio (V_D/V_T), decrease in P_{aO_2}, and statistically but not clinically significant alteration of arterial oxygenation indexes were noted. However, when patients with COPD, restrictive disorders, and neuromuscular disease were compared, significant changes in arterial oxygenation parameters were found only in patients with restrictive disorders. There were significant decreases in heart rate, systolic pulmonary artery pressure, and pulmonary capillary wedge pressure when PSV was applied. Oxygen transport and oxygen consumption were unchanged. CONCLUSIONS: PSV could be a possible alternative to A/C ventilation in patients with respiratory failure. PSV caused an increase in V_D/V_T in association with a significantly lower pressure in the airway and I:E ratio. Randomized studies are needed to define the long-term benefits of both respiratory modes and the conditions in which PSV may be a valuable alternative to A/C ventilation.

Increased Mortality of Older Patients with Acute Respiratory Distress Syndrome—MR Suchyta, TP Clemmer, CG Elliott, JF Orme Jr, AH Morris, J Jacobson, R Menlove. Chest 1997; 111(5):1334.

OBJECTIVE: To examine the relationsh between age and mortality in ARDS patien d

evaluate the importance of factors that increase the mortality of older ARDS patients. DESIGN: Prospective inception cohort study. SETTING: Community-based referral hospital. PATIENTS: Two hundred fifty-six ARDS patients identified from May 1987 to December 1990. ARDS was defined by the following: (1) $P_{aO_2}/P_{AO_2} \leq 0.2$; (2) pulmonary capillary wedge pressure ≤ 15 mm Hg; (3) total static thoracic compliance ≤ 50 mL/cm H_2O; (4) bilateral infiltrates on chest radiograph; and (5) an appropriate clinical setting for ARDS. MAIN OUTCOME MEASURES: Comparison of organ failure, incidence of sepsis, patient demographics, arterial oxygenation, and level of support in those 55 years and younger and those older than 55 years of age. Withdrawal of support in patients who died. RESULTS: Seventy-two of 112 patients older than 55 years (64%) died versus 65 of 144 patients 55 years and younger (45%) ($p = 0.002$). Examination of patient groups using age identified older than 55 years as a "cutpoint" above which mortality was greater ($p = 0.002$). Older nonsurvivors did not differ from nonsurvivors 55 years or younger with respect to gender, smoking history, ARDS risk factors, ARDS identifying characteristics, APACHE II (acute physiology and chronic health evaluation), number of organ failures, or the incidence of sepsis. In the 48 hours prior to death, nonsurvivors 55 years and younger had more organ failure (3.4 ± 0.2 vs 2.8 ± 0.2; $p = 0.03$), higher fraction of inspired oxygen (0.82 ± 0.03 vs 0.68 ± 0.03; $p = 0.008$), and higher positive end-expiratory pressure levels (13 ± 1 vs 8 ± 1; $p = 0.001$) than older nonsurvivors. Despite more severe expression of disease, only 32 (50%) nonsurvivors 55 years and younger had support withdrawn. Significantly more nonsurvivors older than 55 years (73%) had support withdrawn ($p = 0.009$). Even in the absence of chronic disease states, withdrawal was more likely for patients older than 55 years (21/51) than in those 55 years and younger (3/32; $p < 0.001$). CONCLUSIONS: Mortality is significantly higher for patients with ARDS older than 55 years. Decisions to withdraw support are made more often in ARDS patients older than 55 years. These data suggest that age bias may influence decisions to withdraw support.

Retreatment Tuberculosis Cases: Factors Associated with Drug Resistance and Adverse Outcomes—AL Kritski, LS Rodrigues de Jesus, MK Andrade, E Werneck-Barroso, MAMS Vieira, A Haffner, LW Riley. Chest 1997;111(5):1162.

OBJECTIVE: Risk factors associated with treatment failure and multidrug-resistant tuberculosis (MDR-TB) were examined among HIV-seronegative patients who were previously treated for tuberculosis (TB). DESIGN: Prospective, cohort study of patients referred to the study hospital for retreatment of TB between March 1986 and March 1990. PATIENTS: The patients belonged to 3 groups, according to outcomes following their previous treatment: 37 patients who abandoned treatment or suffered relapse after completion of therapy (group A), 91 patients who failed to respond to the first-line drug regimen (group B), and 78 patients who failed to respond to the second-line drug regimen (group C). RESULTS: Patients with *Mycobacterium tuberculosis* strains resistant to rifampin and isoniazid were found in 2 (6%) in group A, 29 (33%) in group B, and 49 (65%) in group C. Cure was achieved in 77% in group A, 54% in group B, and 36% in group C. Death occurred in none of the patients in group A, 8% in group B, and 24% in group C. In a multivariate logistic regression analysis, unfavorable response (failure to sterilize sputum culture, death, and abandonment) was significantly associated with infection with a multidrug-resistant *M. tuberculosis* strain ($p = 0.0002$), cavitary disease ($p = 0.0029$), or irregular use of medications ($p < 0.0001$). CONCLUSION: These observations show that a previous treatment outcome and current clinical and epidemiologic histories can be used to predict the development of MDR-TB and adverse outcomes in patients undergoing retreatment for TB. Such information may be useful for identifying appropriate patient candidates for programs such as directly observed therapy. *See the related editorial:* ***'Multidrug'-Resistant Tuberculosis: It Is Time To Focus on the Private Sector of Medicine****—JA Sbarbaro. Chest 1997;111(5):1149-1151.*

Noncompliance with Directly Observed Therapy for Tuberculosis: Epidemiology and Effect on the Outcome of Treatment—WJ Burman, DL Cohn, CA Rietmeijer, FN Judson, JA Sbarbaro, RR Reves. Chest 1997;111(5):1168.

OBJECTIVES: To describe the epidemiology and clinical consequences of noncompliance with directly observed therapy (DOT) for treatment of tuberculosis. DESIGN: Retrospective review. SETTING: An urban tuberculosis control program that emphasizes DOT. PATIENTS: All patients treated with outpatient DOT from 1984 to 1994. MEASUREMENTS & RESULTS: We defined noncompliance as follows: (1) missing ≥ 2 consecutive weeks of DOT; (2) prolongation of treatment >30 days due to sporadic missed doses; or (3) incarceration for presenting a threat to public health. Poor outcomes of therapy were defined as a micro-

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biologic or clinical failure of initial therapy, relapse, or death due to tuberculosis. Fifty-two of 294 patients (18%) who received outpatient DOT fulfilled one or more criteria for noncompliance. Using multivariate logistic regression, risk factors for noncompliance were alcohol abuse (odds ratio, 3.0; 95% confidence interval, 1.2 to 7.5; p = 0.02) and homelessness (odds ratio, 3.2; 95% confidence interval, 1.5 to 7.2; p = 0.004). Noncompliant patients had poor outcomes from the initial course of therapy more often than compliant patients: 17 of 52 (32.7%) versus 8 of 242 (3.3%); relative risk was 9.9; 95% confidence interval was 4.5 to 21.7 (p < 0.001). CONCLUSIONS: In an urban tuberculosis control program, noncompliance with DOT was common and was closely associated with alcoholism and homelessness. Noncompliance was associated with a 10-fold increase in the occurrence of poor outcomes from treatment and accounted for most treatment failures. Innovative programs are needed to deal with alcoholism and homelessness in patients with tuberculosis. *See the related editorial:* ***Beyond Directly Observed Therapy for Tuberculosis****—CM Nolan. Chest 1997;111(5):1151-1153.*

The Effects of Cigarette Smoking and Gestational Weight Change on Birth Outcomes in Obese and Normal-Weight Women—WL Hellerstedt, JH Himes, M Story, IR Alton, LE Edwards. Am J Public Health 1997;87(4):591.

OBJECTIVES: The associations of infant birth outcomes with maternal pregravid obesity, gestational weight gain, and prenatal cigarette smoking were examined. METHODS: A retrospective analysis of 1,343 obese and normal-weight gravidas evaluated the associations of cigarette smoking, gestational weight change, and pregravid body mass index with birthweight, low birthweight, and small- and large-for-gestational-age births. RESULTS: Smoking was associated with the delivery of lower-birthweight infants for both obese and normal-weight women, and gestational weight gain did not eliminate the birthweight-lowering effects of smoking. Women at highest risk of delivering lower-birthweight infants were obese smokers whose gestational gains were less than 7 kg and normal-weight smokers whose gestational gains were less than 11.5 kg. CONCLUSIONS: To balance the risks of small and large-size infants, gains of 7 to 11.5 kg for obese women and 11.5 to 16 kg for normal-weight women appear appropriate. *See the related editorial:* ***Annotation: Cigarette Smoking, Nutrition, and Birthweight****—KM Rasmussen, B Adams. Am J Public Health 1997;87(4):543-544.*

Pulse Oximetry as a Fifth Pediatric Vital Sign—WR Mower, C Sachs, EL Nicklin, LJ Baraff. Pediatrics 1997;99(5):681.

PURPOSE: To determine the utility of pulse oximetry as a routine fifth vital sign in acute pediatric assessment. DESIGN: Prospective study using pulse oximetry to measure oxygen saturation in children presenting to emergency department triage. Saturation values were disclosed to clinicians only after they had completed medical evaluations and were ready to discharge or admit each child. We measured changes in medical treatment and diagnoses initiated after the disclosure of pulse oximetry values. SETTING & PARTICIPANTS: The study included 2,127 consecutive children presenting to triage at a university emergency department. MEASUREMENTS: Changes in select diagnostic tests: chest radiography, complete blood count, spirometry, arterial blood gases, pulse oximetry, and ventilation-perfusion scans; treatments: antibiotics, β-agonists, supplemental oxygen; and hospital admission and final diagnoses that occurred after disclosure of triage pulse oximetry values. RESULTS: Of 305 children having triage pulse oximetry values less than 95%, physicians ordered second oximetry for 49, additional chest radiography for 16, complete blood counts for 7, arterial blood gas measurements for 4, spirometry for 2, and ventilation-perfusion scans for 2. Physicians ordered 39 new therapies for 33 patients, including antibiotics for 15, supplemental oxygen for 11, and β-agonists for 8. Five patients initially scheduled for hospital discharge were subsequently admitted. Physicians changed or added diagnoses in 25 patients. CONCLUSIONS: Using pulse oximetry as a routine fifth vital sign resulted in important changes in the treatment of a small proportion of pediatric patients.

Yield from Flexible Bronchoscopy in Children—S Godfrey, A Avital, C Maayan, M Rotschild, C Springer. Pediatr Pulmonol 1997; 23:261.

Flexible fiberoptic (FO) bronchoscopy can now be undertaken readily in children using topical anesthesia and light sedation and has largely supplanted rigid open tube (OT) bronchoscopy for diagnostic purposes. The present study examined the contribution of the FO bronchoscope to clinical management in children presenting with specific types of problems. We examined the first 200 consecutive flexible bronchoscopies performed in 1995 in children under 18 years of age (median age, 2.27 years). Indications for bronchoscopy were noisy breathing (26.5%), recurrent pneumonia (21.0%), suspected pneumonia in an immunocompromised patient (10.5%), atelectasis or bronchial toilet (12.5%), possible foreign body aspiration (13.0%), and miscellaneous other reasons (16.5%). Inspection of the airway was abnormal in 67.0% of all investigations and made a clinically meaningful contribution to management in 67.5%, especially in those with noisy breathing (98.1%), possible foreign body aspiration (100%), and atelectasis (76.0%). Bronchoalveolar lavage (BAL) cytology was abnormal in 80.4% of the 107 lavages, but contributed little to management except in those with recurrent pneumonia (73.8%). Bacteria were isolated in 26.6% of the 109 specimens cultured, but this finding rarely affected management. Fungi were isolated in 47.4% of the 19 lavages in the immunocompromised group. Together, inspection, BAL, and microbiology contributed to management in a mean of 90.5% (range, 76.2-100%) of patients in the various groups. We concluded that a high yield of clinically meaningful information can be expected from FO bronchoscopy in children when coupled with BAL and microbiological studies of lavage fluid.

Repeatability of Methacholine Challenges in 2- to 4-Year-Old Children with Asthma, Using a New Technique for Quantitative Delivery of Aerosol—B Klug, H Bisgaard. Pediatr Pulmonol 1997; 23:278.

To determine the repeatability of bronchial responsiveness in awake young children, 2 methacholine challenge tests were performed on separate days in 16 children with stable asthma (mean age, 3-3/4 years). Methacholine was administered using a new method for quantitative delivery of aerosol that eliminates the effect of dilution of the aerosol by entrainment of air and enables quantitative delivery of aerosol according to body weight. Respiratory function was monitored by measurement of respiratory resistance by the interrupter technique (Rint), respiratory resistance and reactance at 5 Hz (Rrs5, Xrs5) by the impulse oscillation technique, transcutaneous measurements of oxygen ($PtcO_2$), and specific airway resistance (sRaw). Repeatability was evaluated by determining the provocative dose that caused a defined percentage of change relative to baseline (PD%: Rint PD_{30}, Rrs5 PD_{30}, Xrs5 PD_{80}, $PtcO_2$ PD_{10}, and sRaw PD_{50}). Repeatability was estimated from the difference between the PD_{x} obtained at the time of the 2 tests. Using the numeric value of these differences, the repeatability of Xrs5 PD_{80}, $PtcO_2$ PD_{10}, and sRaw PD_{50} was [mean (SD)]: [0.8 (0.5)] [0.5 (0.4)] and [0.7 (0.6)] doubling doses, respectively. Rint PD_{30} and Rrs5 PD_{30} proved to be less reproducible: [1.2 (1)] and [1.6 (0.9)] doubling doses, respectively. The new method of aerosol delivery offers a means of standardizing the bronchoconstrictor stimulus, and the results show that estimates of bronchial responsiveness in young children can be obtained reproducibly within one doubling dose of methacholine.

Retrospective Review of the Effects of rhDNase in Children with Cystic Fibrosis—J Davies, M-T Trindade, C Wallis, M Rosenthal, O Crawford, A Bush. Pediatr Pulmonol 1997;23:243.

Trials of rhDNase in mixed groups of adults and children with cystic fibrosis (CF) have demonstrated improvements in lung function and well-being. This has led to many pediatric CF patients receiving regular rhDNase therapy although their response to treatment may not be the same as that seen in adults. We have retrospectively reviewed

the effects of rhDNase during the first year of therapy in 65 children receiving the drug at 2 tertiary referral centers. Outcome measures included changes in lung function, oxygen saturation, use of intravenous antibiotics, and subjective improvement. Median baseline lung function (% of predicted) was 45% for forced expiratory volume in 1 second (FEV_1) and 58% for forced vital capacity (FVC). At 3-4 months following initiation of therapy the group demonstrated median (95% CI) increases of 14.2% (95% CI 7.3; 21.1%) in FEV_1 and 7% (0; 14%) in FVC. Within this wide scatter of responses, one-quarter of children deteriorated, but almost 50% showed significant improvements of > 10%. A similar pattern was seen at 9 months, with median increases for the group of 11.1% (0; 18.8%) in FEV_1 and 5.6% (0; 17%) in FVC, again with approximately one-third of the group deteriorating and one-half improving significantly. Intravenous antibiotic use decreased significantly. Almost all the children (89%), including those with a fall in lung function, described subjective improvement. There were no predictive markers at baseline of a good response to the drug. However, there was a good correlation between lung function response at 3 months and that at 6, 9, and 12 months. Thus, children respond to rhDNase at least as well as adults, and a therapeutic trial is justified in those over 5 years with significantly impaired lung function. Response is highly variable, making careful individual assessment mandatory. Baseline characteristics are not useful in predicting those children who will respond well to treatment, but long-term response to the drug can be predicted on the basis of spirometric improvement at 3 months. Therefore, this would be a useful time period for a therapeutic trial.

Outcome and Acute Care Hospital Costs after Warm Water Near Drowning in Children—DW Christensen, P Jansen, RM Perkin. Pediatrics 1997;99(5):715.

OBJECTIVE: Predictive efforts using individual factors or scoring systems do not adequately identify all intact survivors, and therefore all drowning victims are aggressively resuscitated in most emergency departments. More reliable outcome prediction is needed to guide early treatment decisions. METHODS: The charts of 274 near drowning patients admitted to Loma Linda University Children's Hospital were retrospectively reviewed. Patient outcome was categorized into good (near normal function), and poor (vegetative or dead) categories. Discriminant analysis was used to identify combinations of variables most able to predict outcome and a clinical classification system was constructed. The acute care hospital costs for each group were compared. RESULTS: Discriminant analysis classification achieved 95% accuracy, predicting death in 6 intact survivors. No combination of variables could accurately separate all intact survivors from the vegetative and dead groups. The clinical classification method achieved 93% overall accuracy, predicting death in 5 intact survivors. Of patients predicted to have a poor outcome, 5 (6.3%) survived intact. Children may experience an unpredictable, prolonged vegetative state followed by full recovery. Vegetative patients are the most expensive to care for (consuming 53% of total costs) while intact survivors are the least expensive. The majority of costs were spent on patients with poor outcome. CONCLUSIONS: Individual outcome cannot be reliably predicted in the emergency department; therefore, aggressive resuscitation of near drowning victims should be performed. Decisions to subsequently withdraw life support should be made based on integration of likelihood of survival, high (but not absolute) certainty, and parental/societal issues. The vegetative patients are the most expensive to care for, while intact survivors are least expensive. Reduction of expenditures on patients likely to have vegetative or dead outcome would result in substantial savings, but loss of normal survivors.

Tolerance To the Bronchoprotective Effect of Salmeterol in Adolescents with Exercise-Induced Asthma Using Concurrent Inhaled Glucocorticoid Treatment—FER Simons, TV Gerstner, MS Cheang. Pediatrics 1997;99(5):655.

OBJECTIVES: The long-acting β_2-adrenergic agonist salmeterol prevents exercise-induced asthma, but tolerance may develop to its bronchoprotective effect. We wanted to ascertain if the development of tolerance could be prevented by using a low-dose treatment regimen of 50 μg once daily, instead of the usual dose of 50 μg twice daily, in adolescents receiving regular glucocorticoid inhalations. METHODS: In a randomized, double-blind, 2 × 28-day crossover study, we administered salmeterol (50 μg) or placebo once daily via a metered-dose inhaler and Nebulizer Chronolog device to monitor compliance. Exercise challenge tests were performed 1 and 9 hours after salmeterol or placebo inhalation on the 1st and 28th day of each treatment period. The primary outcome variable was the maximum decrease in percent predicted FEV_1 postexercise. RESULTS: Fourteen subjects with a mean age of 13.1 years completed the study. The first dose of salmeterol had an excellent bronchoprotective effect against exercise-induced asthma at 1 and 9 hours. After the 28th consecutive daily dose of salmeterol, the bronchoprotective effect was significantly greater than that of placebo at 1 hour, but not at 9 hours. CONCLUSIONS: We conclude that a single 50-μg dose of salmeterol has an excellent protective effect against exercise-induced asthma for at least 9 hours, but that this effect may wane during regular once-daily salmeterol treatment, despite the reduced frequency of dosing and despite concomitant use of inhaled glucocorticoids.

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Will We Take the High Road? The Respiratory Care Profession's Approach to the Future

Some of my colleagues and I have concerns regarding the future of the respiratory care profession. The January Issue of the Journal addressing "Emerging Health Care Delivery Models and Respiratory Care" serves the respiratory care community well. I personally have distributed many copies of Sam Giordano's Conference Summary[1] to respiratory care practitioners (RCPs) working throughout our rehabilitation network and have strongly advised our staff to consider Mr Giordano's comments as an excellent, motivating forecast.

In 1998, I will celebrate 20 years as a respiratory care practitioner. For the last 8 years, I have had the opportunity to work as a program manager in a rehabilitation hospital, serving well over 250 patients with chronic respiratory illnesses, each year. I believe that the value added by the respiratory care practitioner to the long-term care of this patient population can be measured in clinical, social, and economic terms. Yet, a number of the skills required to provide continuing inpatient and outpatient care to chronic lung patients are not a part of the curriculum of many respiratory therapy programs. My firsthand experience tells me that the skill set for chronic obstructive pulmonary disease (COPD) management includes didactic and practical knowledge of exercise physiology, nutrition, psychosocial assessment, third-party reimbursement, and the planning of integrated care.

During the years that I have worked in postacute environments, I have become aware of a subset of highly skilled, compassionate RCPs who have shouldered the responsibility for broadening their skills to be effective caregivers in this setting. Because of this group, I have developed great pride in our profession and I admire its integrity. But, a potential problem looms on the horizon. To assure our survival, RCPs have constantly sought mechanisms to demonstrate our added value to the organization by which we are employed. Over the years, several types of added value have emerged including financial (revenue generating or cost reducing) and clinical (improved outcomes in biopsychosocial domains.)

Many of us remember and others of us have been told of the pre-diagnosis related group (DRG) era of the 1970s when respiratory care departments were able to contribute a considerable percentage to each hospital's net revenue. As a colleague remembered recently, it was once possible to compensate for 6-figure losses simply by adjusting the oxygen charge upward by a few pennies per hour. The reimbursement climate of "if we charge for it, they will pay" endeared us to our administrators; yet our clinical value was at times questioned by other caregivers, the perception being that we existed only to generate revenue for the hospital.

Following the implementation of the DRG system, we became a cost burden to the acute care hospital and began to seek other mechanisms for demonstrating our value. Through further definition of our role we have illustrated that we are highly skilled, multiskilled caregivers. With the implementation of therapist-driven protocols, changes in technology, and increases in our skill set, we have gained the respect and acknowledgment of our colleagues as necessary components of the health care team. The value we add has been demonstrated by reductions in the number of unnecessary procedures and therapy,[2,3] improved clinical outcomes,[4,5] and enhancements to quality of life[6,7] in selected patient populations.

However, certain members of our profession have sought other methods of assuring their economic survival. The many changes in third-party-reimbursement regulations have resulted in successful economic outcomes being measured differently by acute care hospitals, rehabilitation hospitals, sub-acute facilities and home care agencies, because the financial incentives are inconsistent. With regard to Medicare patients, acute care hospitals measure a successful financial outcome by discharging the patient below the DRG length-of-stay average for their geographic area. Rehabilitation hospitals and long-term acute-care hospitals (LTAC) are DRG exempt. These institutions are paid based on the average cost per case assessed under the Tax Equality Financial Responsibility Act (TEFRA)[8] and are often capable of treating a patient for longer periods of time (length of stay) while remaining profitable. Skilled nursing facilities (SNFs) are reimbursed under separate Medicare regulations wherein each patient is able to receive 20 days of complex medical care within the SNF without co-pay responsibility.[9] Home health organizations are reimbursed for clinician visits; the greater the number of visits, the more profitable the organization (similar to pre-DRG acute hospital reimbursement for ancillary services), although there is no existing reimbursement for RCP visits through home health agencies.

One can appreciate that the incentives across the continuum of care do not allow for successful vertical integration of providers; wherein the acute facility needs to discharge

the patient as soon as possible to whatever venue is available, rehabilitation and LTAC facilities have an incentive to constantly adjust lengths of stay to assure reported cost variables coincide with government audit. Skilled nursing facilities have an incentive to average a 21-day length of stay; and home health agencies need to maximize the number of visits, therefore, having little initiative to refer patients to outpatient programs.

The ever-creative entrepreneur has developed strategies to maximize reimbursement for the services of RCPs. Because DRG-exempt mechanisms for reimbursement for respiratory care exist, many RCPs have been shifted out of the acute care environment into the postacute venue. This is not counterproductive in the patient care sense, but it may threaten us with regard to how we are perceived by our colleagues in other professions, third-party payers, and HCFA.

The tasks that we are deployed to perform in the postacute environment must not regress to basic floor therapy procedures. The criteria for Medicare reimbursement for respiratory care in the SNF include the prerequisite demonstration of a need for the level of clinical skill.[8] For example, providing a bronchodilator treatment by small volume nebulizer can be either a maintenance task or an intervention, prescribed under a therapist-driven protocol, for the alleviation of bronchospasm and monitoring of therapeutic effect. The simple maintenance treatment may be administered by less skilled health care workers or by patients themselves, and rightly so! Under such circumstances, Medicare would not reimburse the SNF for the time required for the RCP to administer the medication. However, if the patient presents with a history of chronic respiratory illness, labile respiratory status, and a need for education, the RCP is considered a beneficial adjunct to the patient care team for patient assessment, therapeutic prescription, monitoring of clinical outcome, and patient education. In this case, Medicare reimburses the SNF for the RCP's time as an ancillary service so long as a transfer agreement is in place.[10] The contrast between these scenarios is subtle, and because it is, it should be obvious that with careful 'documentation' it would be easy to improve the income to a SNF through contract respiratory services. But, do we as a profession want to risk all that we have worked for simply to generate short-term revenue for a facet of health care that is temporarily exempt from prospective payment systems?

Our facility serves as a clinical training site for students enrolled in a local 2-year program. Many of these students and some of our staff members have per-diem employment arrangements with large national long-term acute care, skilled nursing and home health corporations. I have recently been shocked by hearsay from many of these clinicians. Given these verbal reports it is quite possible that RCPs are now being influenced to alter medication dosing and frequency schedules to assure compliance with Medicare guidelines for reimbursement to the SNF regarding care delivered by a respiratory therapist.

We should not forget the criticism, approaching ridicule (and perhaps not always deserved), that our profession received in the 1970s related to our involvement in and defense of unneeded intermittent positive pressure breathing, or IPPB, therapy.[11-18] I remember working for a 500-bed hospital in southern California that actually employed a full-time therapist to solicit therapy orders from attending physicians. That kind of behavior is once again rearing its ugly head in our profession through what I choose to call the 'cottage industry' of postacute care.

The postacute care industry is a natural business segue to the nonuniform cost control efforts of the Federal government and its contracted intermediaries. A physician colleague proudly told me recently of his critical path for ventilator patients, explaining that for the first time in years his hospital was operating 'in the black' under the DRG for the ventilator-dependent COPD patient. He further related that his facility had made arrangements for the rapid transfer of ventilator-dependent patients to a local postacute facility.

It is not enough to establish a critical path within the acute-care facility that quickly shunts the ventilator-dependent COPD patient to the postacute facility in a way that keeps the facility 'in the black' without studying the cost-effectiveness and cost-benefit implications of such a maneuver for the whole system. This example illustrates the confused perspective of health care providers in our country. The primary objective of the facility was to discharge the patient below the DRG break-even length of stay. From the government's perspective, the facility was shifting reimbursement from one provider to the next. The long-term cost benefit to society of such a strategy remains to be seen.

My heartfelt call to respiratory care practitioners, educators, and, perhaps most importantly, the providers of our services is, Please consider the future! Our delivery systems are evolving. Several factors influence the demand for change, the prime stimulus perhaps being the disproportionate increase in health care expenditure and the consequent need to control costs. As legislation has been introduced, human elements have clouded the focus; mixed economic incentives, confusion over the definition of positive biopsychosocial outcomes, passion for and fear of loss of professional security. As caregivers, we have the opportunity to help shape the future of health care. We can, in fact, have a part in engineering the systems that will care for our society for future generations. To accomplish this task, it is imperative that we collaborate, focus on the needs of each patient population beyond the limited scope of our point of care, adhere to a value system that carefully balances economic, clinical, and societal outcomes and considers the stability of those who follow us—the 'seventh generation' alluded to in Native American culture.

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Isolation Valve Increases Work of Breathing in a Mechanically Ventilated Pediatric Animal Model

Richard T Fiser MD, Adalberto Torres Jr MD MS, Shirley Holt RRT, Sterling Wilson MS, and Mark J Heulitt MD

BACKGROUND: Accurate measurement of minute ventilation and, hence, the accurate calculation of oxygen consumption ($\dot{V}_{O_2}$), using open-circuit indirect calorimetry may require separation of inspired and expired gases with an isolation valve when continuous bias flow is present. We hypothesized that the use of an isolation valve in the ventilator circuit would increase work of breathing (WOB). METHODS: We studied the effect of a valve apparatus on WOB in 5 mechanically ventilated, spontaneously breathing, healthy lambs. Animals were ventilated with a continuous-flow, volume ventilator (F_{IO_2} 0.21, pressure support 5 cm H_2O). WOB of the animal (WOB_{pt}) and pressure-time product (PTP) were determined with a Bicore CP-100 respiratory monitoring device. RESULTS: WOB and PTP were elevated by approximately 100% with the isolation valve present ($p = 0.04$). CONCLUSIONS: We conclude that the use of this isolation valve to separate inspired and expired gases significantly increases WOB in intubated healthy lambs. We speculate that this increase in WOB may be associated with increased $\dot{V}_{O_2}$ in critically ill patients, thereby altering the results of metabolic monitoring. [Respir Care 1997;42(7):688-692]

Introduction

Bedside indirect calorimetry is a clinically applicable technique for monitoring oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), respiratory quotient (RQ), and the adequacy of nutritional support in the dynamic environment of an intensive care unit.[1-3] Metabolic monitoring with indirect calorimetry is noninvasive and entails minimal risk to the patient. However, the measurement of metabolic variables using indirect calorimetry in mechanically ventilated patients is technically demanding and has great potential for inaccuracies. Accurate measurement of expired volume and gas concentrations, and, hence, the accurate calculation of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ has been reported to require the separation of inspired and expired gases to prevent dilution of exhaled gases by the compressible volume of the circuit and/or continuous bias flow.[1-3] The separation of inspired and expired gases can be achieved with an isolation valve consisting of inspiratory and expiratory diaphragms or 1-way valves.[2,3] Such an apparatus may increase mechanical dead space, and the 1-way valves may change the characteristics of flow through the circuit. Branson[1] and Head and colleagues[2] have suggested that the addition of a valve may increase imposed WOB, but this has not been adequately studied. We hypothesized that an isolation valve significantly increases WOB in mechanically ventilated, spontaneously breathing lambs.

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Materials & Methods

This study was approved by the Animal Review Committee of the University of Arkansas for Medical Sciences. Animals were cared for in accordance with the standards for care and use of laboratory animals set forth by the University.

Model Preparation

We used 5 healthy 4- to 5-week-old Dorsett-Western Cross lambs, each weighing approximately 10 kg, for the experiments. These lambs were selected because their respiratory rate, tidal volume, and minute ventilation are comparable to those of pediatric patients. Animals were studied as previously described by Heulitt et al.[4] Vascular catheters were surgically placed via cutdown into the external jugular vein for drug administration and into the internal carotid artery for continuous blood pressure monitoring. The animals were allowed to recover for 24-48 hours after surgery prior to the initiation of studies. On each study day, the animal was anesthetized with intravenous midazolam, 0.25 mg/kg, and propofol, 0.3 mg/kg, prior to endotracheal intubation with a cuffed endotracheal tube (ETT) with an inner diameter of 5.0 mm. The cuff was inflated to prevent air leak. After intubation, the lamb was placed into a sling mounted in a thermally controlled chamber. A heat/moisture exchanger* (HME, Humidivent 600) was attached directly to the ETT in order to protect the expiratory pneumotachometer from excess moisture. The lambs received continuous intravenous sedation via the external jugular venous catheter to maintain a level of sedation at which the animal was asleep and breathing spontaneously and returned to sleep spontaneously after stimulation. This level of sedation was typically achieved with infusion rates of midazolam of 0.3 mg/kg/h and propofol of 10 mg/kg/h.

Continuous monitoring of the animal's heart rate, respiratory rate, arterial blood pressure, temperature, and pulse oximeter oxygen saturation was performed. Esophageal pressure (P_{es}), an estimate of intrapleural pressure, was measured with a balloon catheter inserted into the esophagus. Correct positioning of the esophageal catheter was confirmed using the occlusion test,[5] during which the animal's proximal airway is occluded and the change in airway pressure is assessed along with the change in P_{es} during spontaneous respiratory effort. If the pressure deflections are of equal magnitude, the esophageal catheter is confirmed to be optimally placed.[5]

Equipment Setup

The animals were ventilated using a Servo 300 ventilator (SV-300). All lambs were ventilated using the pediatric option, which provides 1 L/min continuous bias flow and an inspiratory flow of 30 L/min to maintain set pressure when the demand valve is triggered.[6] All studies were conducted using flow-triggering, with the sensitivity set in the "green zone" on the SV-300. When the pointer of the sensitivity dial rests in the green zone, a ventilator breath is initiated when the patient's effort causes a brief drop in flow of 0.3-1 L/min when the pediatric mode is in use.[6] All lambs were studied using pressure support (PS) ventilation with PS of 5 cm H_2O and an F_{IO_2} of 0.21. Inspiratory rise time was set at 5%.

WOB with and without the isolation valve was determined using a Bicore CP-100 respiratory monitor. The monitor's flow transducer was placed between the Y-piece of the breathing circuit and the HME to measure mean airway pressure (P_{aw}) and the accumulation of flow in order to determine volume. For studies with the valve, a 2-way, T-shaped nonrebreathing valve was placed in line with the inspiratory and expiratory limbs of the ventilator circuit (Fig. 1). During studies with the isolation valve, the bypass tubing seen in Figure 1 was unclamped to allow bias flow to continue uninterrupted during exhalation when the inspiratory valve was closed. During control studies, the isolation valve was replaced by the circuit Y-piece, and the bypass tubing was clamped. Use of the bypass tubing allowed us to use the same circuit for studies with and without the valve. The esophageal balloon and flow transducer were connected to the respiratory monitor, which provided real time display of respiratory variables including tidal volume (V_T), WOB of the lamb (WOB_{pt}), WOB by the ventilator (WOB_v), positive end-expiratory pressure (PEEP), intrinsic PEEP, airway resistance, and pressure-time product (PTP). These data were collected for each breath and continuously downloaded to a notebook computer. WOB_{pt} was calculated by integrating the area of the P_{es}-V_T loop from the start of inspiration either until the end of inspiration or until inspiratory P_{es} became greater than end-expiratory P_{es}.[7]

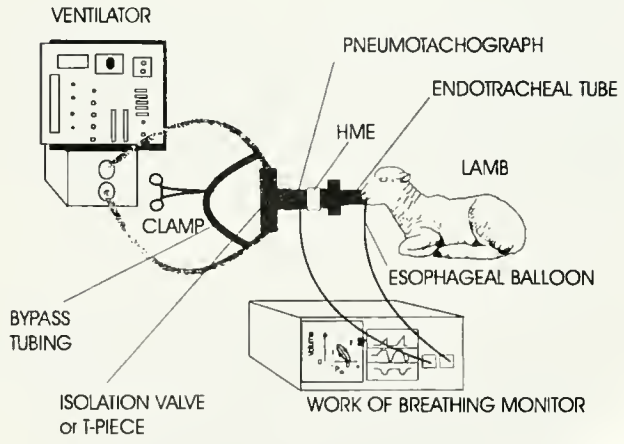

Fig. 1. Diagram of equipment set-up (HME = heat moisture exchanger).

*Suppliers of commercial products are listed in the Product Sources section at the end of the text.

WOB_v was calculated by integrating the area of the airway pressure-volume loop. PTP was calculated by integrating P_{es} (end-expiratory P_{es} – current P_{es}) and time for the duration of contraction of the respiratory muscles (current V_T/chest-wall compliance).[7] Chest-wall compliance was assumed to be 200 mL/cm H_2O.

Study Design & Statistics

Each animal was used as its own control and studies were conducted in random order, using a random number table. Fifty breaths with and without the valve from each animal were chosen for analysis; the third set of 50 breaths/study animal was arbitrarily chosen for analysis. Descriptive statistics were performed for WOB_{pt} and PTP and 95% confidence intervals calculated.[8] The mean values for WOB_{pt} and PTP with and without the valve were compared by the Wilcoxon signed rank test for significant differences, using commercially available statistical software, SPSS for Windows. A p value < 0.05 was considered significant.

Results

WOB_{pt} and PTP were significantly elevated when the isolation valve was used. Values are shown in Table 1 and in Figures 2 and 3. Despite the marked increase in WOB and PTP, no changes were apparent in the animal's respiratory rate or level of comfort when the isolation valve was in place.

Discussion

This study demonstrates that WOB_{pt} and PTP are significantly elevated during mechanical ventilation by the presence of an isolation valve in the ventilator circuit. The increased WOB caused by the isolation valve may have important implications for the accurate application of metabolic monitoring to clinical practice.

$\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and energy expenditure have important clinical applications in the dynamic environment of critical care. Among these applications are the evaluation of the balance between oxygen supply and demand,[9] measurement of the oxygen cost of breathing as a guide to successful weaning from mechanical ventilation,[10] and the adequacy of caloric support.[11-12] Although indirect calorimetry is noninvasive and relatively safe, it is technically challenging. Continuous bias flow, fluctuating oxygen concentrations, and air leak around the ETT contribute to inaccuracies in measurement of gas volumes and

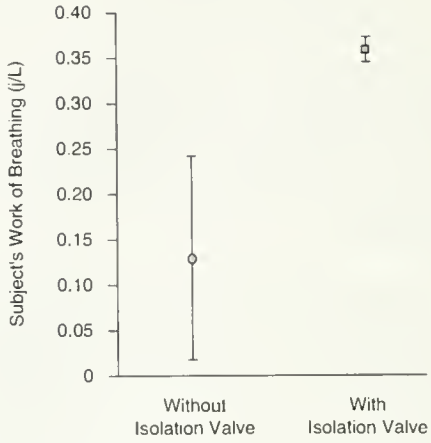

Fig. 2. 95% confidence intervals for work of breathing in lambs; (+) = with isolation valve, (–) = no isolation valve; p = 0.04.

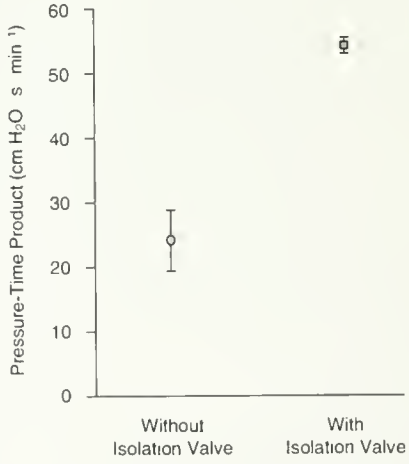

Fig 3. 95% confidence intervals for pressure time product; (+) = with isolation valve, (–) = no isolation valve; p = 0.04.

Table 1. Results of Measurements of Work of Breathing (WOB) and Pressure Time Product (PTP) in 5 Lambs Breathing with (+) and without (–) an Isolation Valve in the Ventilator Circuit

Variable	Mean Value (SD)	95% Confidence Interval
WOB_{pt} (–)	0.13 (0.09) j/L	0.02-0.24 j/L
WOB_{pt} (+)	0.36 (0.01) j/L	0.35-0.37 j/L
PTP (–)	24.46 (10.52) cm $H_2O \cdot s \cdot min^{-1}$	11.40-37.52 cm $H_2O \cdot s \cdot min^{-1}$
PTP (+)	53.94 (2.67) cm $H_2O \cdot s \cdot min^{-1}$	50.63-57.23 cm $H_2O \cdot s \cdot min^{-1}$

concentrations. Separation of inspired from expired gases is often important for the accuracy of mixing chamber measurements.[1] If $\dot{V}_E$, F_{EO_2}, and F_{ECO_2} are rendered inaccurate because of dilution with continuous bias flow or compressible circuit volume, the error in calculation of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ is significant.[1] Some authors therefore recommend the use of an isolation valve during metabolic monitoring with an indirect calorimeter that incorporates a mixing chamber.[1-3]

Branson[1] remarked that an isolation valve was necessary for accurate metabolic monitoring but cautioned that the valve may be associated with an increase in WOB. In their evaluation of an isolation valve system, Head and colleagues[2] stated that the resistance imposed by 1-way valves may affect WOB but that the increase would not appreciably change the result of a metabolic study. In our animal model of mechanically ventilated young children, WOB was significantly elevated by the isolation valve. PTP, an indirect measure of the oxygen cost of breathing, was also markedly increased with the valve. Mechanical dead space may have been a factor in the increased WOB seen with the valve. The isolation valve used in this study has a measured dead space of 15.8 mL, according to the manufacturer's specifications, although the Y-piece used in the circuit has a measured dead space of only 1 mL.

Although we demonstrated a statistically significant increase in WOB with the valve, it could be argued that this finding was not clinically important because we did not measure $\dot{V}_{O_2}$ during the study. Other studies from this institution have documented increases in $\dot{V}_{O_2}$ of approximately 3-4% when WOB_{pt} is elevated by 30-50% in healthy lambs.[13] The roughly 100% increase in WOB_{pt} documented in our study might be associated with an increase in $\dot{V}_{O_2}$ of 6-8%. Such a relatively small increase in $\dot{V}_{O_2}$ is within the range of clinical variability, but it must be emphasized that our model consisted of healthy animals. WOB in healthy subjects is responsible for less than 5% of the total $\dot{V}_{O_2}$.[14] However, as much as 25% of the $\dot{V}_{O_2}$ of ICU patients has been attributed to increased WOB.[15-17] We speculate that a 100% increase in imposed WOB by an isolation valve could significantly skew the results of metabolic monitoring in the critically ill.

Each animal demonstrated a significant increase in WOB_{pt} with the valve, and no overlap existed between the 95% confidence intervals of studies with and without the valve (Figs. 2 & 3). The relatively wide confidence interval for WOB_{pt} without the valve reflects intersubject and intrasubject variability in work of breathing. Despite intersubject variability and the small number of subjects studied, a clear gap exists between the confidence intervals for WOB with and without the valve. The narrow confidence intervals for WOB_{pt} and PTP with the isolation valve lends even more strength to the argument that the imposition of the valve causes all subjects to work significantly harder. Therefore, despite the small number of subjects studied, these results give validity to our conclusions.

Conclusion

The use of a 2-way isolation valve designed to separate inspired and expired gases for metabolic monitoring resulted in significant increases in WOB in our animal model. The additional WOB associated with isolation valves produced by different manufacturers may vary. If not taken into account, the presence of an isolation valve may cause erroneous results in metabolic monitoring, particularly in the critically ill patient.

PRODUCT SOURCES

Heat-moisture exchanger:
Portex Humidivent 600, Portex, Keene NH

Ventilator:
SV-300, Siemens Medical Systems, Piscataway NJ

Respiratory monitor:
Bicore CP-100, Bicore Monitoring Systems, Irvine CA

Isolation valve:
Hans Rudolph Model no. 1410, Hans Rudolph, Kansas City MO

Notebook computer:
DELL 325N, Dell Computer Co, Republic of Korea

Statistical software:
SPSS for Windows 6.0, SPSS Inc, Chicago IL

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A Comparison of the i-STAT System and Corning 278 for the Measurement of Arterial Blood Gas Values

David C Shelledy PhD RRT and Wayne A Smith BS RRT

INTRODUCTION: We compared the performance of a point-of-care measurement system to that of a conventional blood gas analyzer. METHODS: One hundred nineteen arterial blood gas samples from 2 hospitals were analyzed using the i-STAT system and Corning 278 concomitantly. Values were compared using the *t* test for dependent samples and the Pearson product moment correlations ($p < 0.05$), and regression equations were calculated to determine the slope and intercept of the regression line for paired values of pH, P_{aCO_2}, and P_{aO_2}. Mean and standard deviations (SD) were also calculated for the difference between the paired results for each variable. RESULTS: Means and SD for the Corning 278 versus the i-STAT for pH were 7.40 (0.06) versus 7.41 (0.07), for P_{aCO_2} 43.0 (9.9) torr versus 43.4 (10.2) torr and for P_{aO_2} 107.9 (73.1) versus 109.7 (76.6) torr. Regression equations were:

$$\text{i-STAT pH} = -0.2174 + 1.0301 \times \text{Corning pH}$$
$$\text{i-STAT } P_{aCO_2} = -0.1724 + 1.0145 \times \text{Corning } P_{aCO_2}$$
$$\text{i-STAT } P_{aO_2} = -2.138 + 1.0373 \times \text{Corning } P_{aO_2}$$

Small, but statistically significant differences between the 2 instruments for pH ($p = 0.015$) and P_{aCO_2} ($p = 0.017$) were obtained but no significant difference for P_{aO_2} ($p = 0.062$). Significant correlations between values were obtained with the i-STAT when compared to the Corning 278 for pH ($r = 0.9392$; $p < 0.001$), P_{aCO_2} ($r = 0.9804$, $p < 0.001$), and P_{aO_2} ($r = 0.9904$, $p < 0.001$). Mean (SD) differences for the paired results between the 2 systems were −0.005 (0.02) for pH; −0.449 (2.02) torr for P_{aCO_2}, and −1.88 (10.9) for P_{aO_2}. CONCLUSIONS: Results obtained via the i-STAT system correlated well with results obtained with the Corning 278. Small, but statistically significant differences between the 2 instruments on pH and P_{aCO_2} are probably not clinically important. [Respir Care 1997;42(7):693-697]

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A version of this paper was presented by Dr Shelledy during the annual OPEN FORUM at the American Association for Respiratory Care 42nd International Convention and Exhibition, November 3-6, 1996, in San Diego, California.

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Introduction

Background

The gold standard for the assessment of oxygenation, ventilation, and acid-base balance in the clinical setting remains arterial blood gas analysis.[1-3] Conventional blood gas analyzers, however, are relatively large, bulky instruments that must be tethered to a gas system incorporating cylinders for calibration.[2] Conventional analyzers are permanently installed, typically in a blood gas laboratory that is often located some distance from the site of patient care. Blood samples must be

transported to the blood gas laboratory for analysis, thus increasing the time needed to obtain results and reducing efficiency.[4] Recent developments in technology have allowed the development of a new type of analyzer that is highly portable.[4-5] These new devices allow for point-of-care analysis of arterial blood samples, which may improve patient care and efficiency while reducing costs.[4,6-8]

Device Description

The i-STAT system (i-STAT Corp, Princeton NJ) is a point-of-care blood analysis device that allows measurement of arterial blood gas values at the bedside. Several cartridge configurations are available for the analyses of sodium, potassium, chloride, urea nitrogen, glucose, hematocrit, ionized calcium, pH, P_{CO_2}, and P_{O_2} and the calculation of total CO_2 (T_{CO_2}), bicarbonate (HCO_3^-), extracellular base excess (BE_{ecf}), anion gap, and hemoglobin.[9] The i-STAT system has been shown to be accurate, reliable, robust, and simple to operate in near-patient applications for the analysis of sodium, potassium, chloride, urea, glucose, and hematocrit.[10-14] The instrument is a battery-powered, hand-held unit that requires a sample of approximately 100 μL blood and an analysis time of 120 seconds.[9] The system uses biosensors with thin-film electrodes microfabricated on silicon chips.[9] These microelectrodes are incorporated into a single-use disposable cartridge to perform the sample analysis.[9] This cartridge contains all of the components necessary to maintain the system: electrical biosensors, reagents, sampling stylus, and waste container.[9] A mechanical system controls the flow of calibration solution and sample within the cartridge, and an electronic system measures and monitors signals from the biosensors. A liquid crystal display provides prompts, messages, and test results. The unit weighs 520 grams and is 6.41 cm wide, 20.97 cm in length, and 5.21 cm in depth. According to the manufacturer, the i-STAT has a functional range for pH of 6.8-8.0, for P_{CO_2} 10-100 torr, and for P_{O_2} 5-800 torr.[9]

We compared the performance of the i-STAT system to the Corning 278 blood gas analyzer (Ciba Corning Diagnostics Corp, Norwood MA). The Corning 278 is a conventional blood gas analyzer in common use that incorporates traditional chemical and gas electrodes for the measurement of pH (Sanz electrode), P_{CO_2} (Severinghaus electrode), and P_{O_2} (Clark electrode).[2,15-17] It has been used as a standard for comparison in the evaluation of other, newer blood gas analyzers.[15-16]

Methods

We sought to determine whether the i-STAT point-of-care system could be successfully used in place of a traditional analyzer for accurate analysis of arterial blood samples. A total of 119 arterial blood gas samples, obtained at 2 area hospitals, was analyzed using the i-STAT system and the Corning 278 blood gas analyzer. The analyses were performed by staff respiratory care personnel as a part of routine clinical practice. For the i-STAT system, samples were analyzed using the procedure outlined in the product manual.[9] For each i-STAT whole blood analysis, an i-STAT 3+ cartridge was inserted into the analyzer to activate the system, and operator and patient numbers were then entered. For blood gas analysis, each cartridge contains heating elements, a reference electrode, biosensors for measurement of pH, P_{CO_2}, and P_{O_2}, and a buffered aqueous calibration solution (pH 7.43, P_{CO_2} 30 torr, and P_{O_2} 160 torr), which is contained in a pouch within the cartridge.[9] The i-STAT test cycle is activated by placing the cartridge containing the blood sample into the analyzer. During the test cycle, the analyzer presses the front of the cartridge, causing a barb to puncture the pouch containing the calibration solution, which is then released to flow over the sensor array for measurement. When the calibration is completed, the analyzer automatically ejects the calibration solution and introduces the blood sample for analysis. If the cartridge does not calibrate properly, the unit cannot be used.

The analysis sequence varied (analyzers were placed side by side), with the sample being introduced into the Corning 278 or i-STAT system first followed by analysis by the other analyzer within 5 minutes. The results of both analyses were then reported. A 1-2 mL sample was collected in one syringe for both analyses. Blood samples were introduced directly from the sample syringe with the needle removed. No capillary tubes were used. At Hospital A, 3 i-STAT units and 3 Corning 278 units were used, and 70 samples were analyzed over a 2-month period. At Hospital B, 4 i-STAT analyzers and 1 Corning 278 were used, and 49 samples were collected and analyzed over a 1-week period. The i-STAT units at Hospital B were rotated during the study. The Corning analyzers were maintained using the hospital's standard protocol as recommended by the manufacturer for 1- and 2-point calibration, and quality control.[17] The i-STAT units were calibrated electronically, and aqueous buffers were analyzed each shift for quality control purposes.

Mean pH, P_{aCO_2}, and P_{aO_2} values obtained from the 2 instruments were compared using the *t* test for dependent samples to determine whether there were significant differences ($p < 0.05$). Pearson product moment correlations were calculated to determine whether there were significant correlations ($p < 0.05$) between the 2 instruments. Regression equations were calculated to determine the slope and intercept of the regression line for paired values of pH, P_{aCO_2}, and P_{aO_2}. Means and standard deviations (SD) were also calculated for the difference between the paired results for each variable to provide a measure of bias and imprecision for the i-STAT when compared to the Corning 278.[18]

Results

The results of the analysis of the 119 arterial blood samples on the 2 systems are shown in Figure 1. All values were

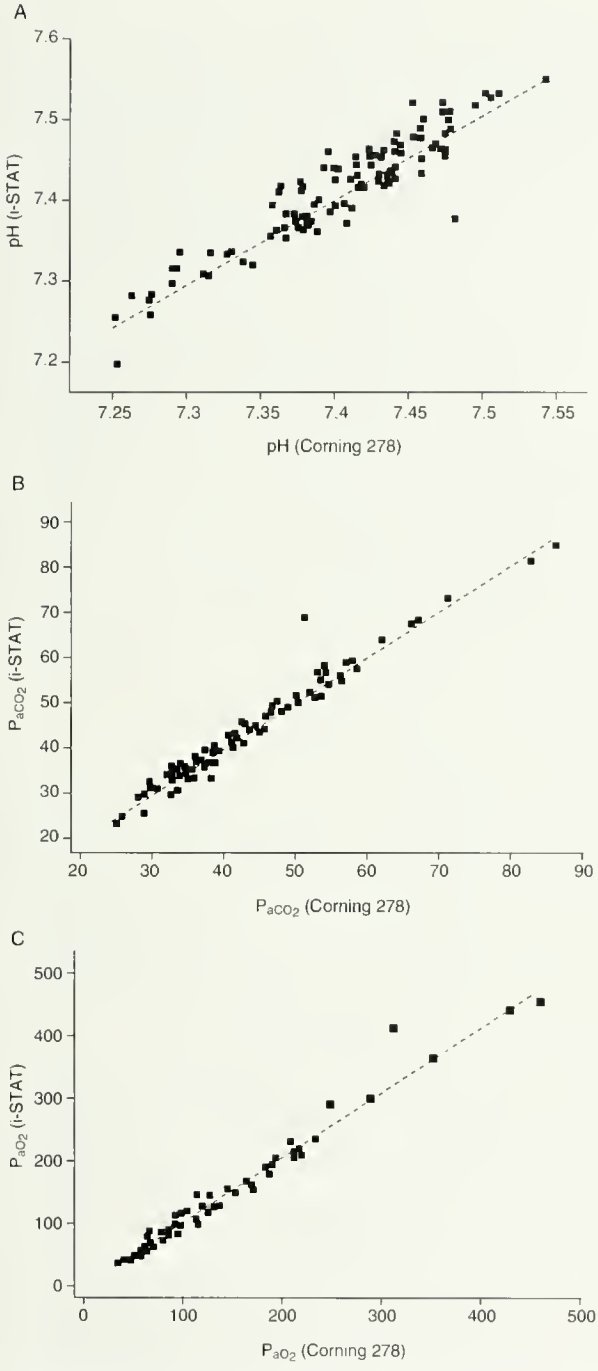

Fig. 1. Plot of values from the analysis of 119 arterial blood samples using the i-STAT (vertical axis) and Corning 278 (horizontal axis) for A. pH, B. P_{aCO_2}, and C. P_{aO_2}.

within the manufacturer's recommended operational range for the i-STAT analyzer, and no correction was made for outliers. Means, SD, and *t* and p values for results from each of the hospitals and the combined data are reported in Table 1. Means and SDs for the individual differences in paired blood gas and pH measurements performed on the i-STAT and Corning 278 for the combined data from both hospitals are shown in Table 2. In Figure 2, the differences between the 2 systems are plotted against the means of the values from each. Regression equations obtained were:

$$\text{i-STAT pH} = -0.2174 + 1.0301 \times \text{Corning pH}$$
$$\text{i-STAT } P_{aCO_2} = -0.1724 + 1.0145 \times \text{Corning } P_{aCO_2}$$
$$\text{i-STAT } P_{aO_2} = -2.138 + 1.0373 \times \text{Corning } P_{aO_2}$$

Table 1. Means, Standard Deviations (SD) and *t* and p Values Comparing pH, P_{aCO_2}, and P_{aO_2} Values Obtained Using the Corning 278 and i-STAT Systems.

Both Hospitals Combined (n = 119)				
	Corning 278	i-STAT	*t*	p
pH	7.40 (0.06)	7.41 (0.07)	−2.47	0.015
P_{aCO_2} (torr)	42.99 (9.9)	43.44 (10.2)	−2.43	0.017
P_{aO_2} (torr)	107.85 (73.1)	109.73 (76.6)	−1.88	0.062
Hospital A (n = 70)				
	Corning 278	i-STAT	*t*	p
pH	7.41 (0.07)	7.42 (0.07)	−2.31	0.024
P_{aCO_2} (torr)	42.50 (11.1)	42.85 (11.1)	−2.25	0.028
P_{aO_2} (torr)	94.79 (50.4)	98.14 (59.7)	−2.07	0.042
Hospital B (n = 49)				
	Corning 278	i-STAT	*t*	p
pH	7.39 (0.05)	7.40 (0.05)	−0.917	0.364
P_{aCO_2}	43.69 (8.0)	44.29 (9.0)	−1.51	0.138
P_{aO_2}	126.50 (94.3)	126.29 (93.9)	0.335	0.739

Table 2. Means and Standard Deviations (SD) of the Individual Differences in 119 Paired Blood Gas and pH Measurements Performed on the i-STAT and Corning 278.

	Mean of the Individual Differences	Standard Deviations ±1 SD	±2 SD
pH	−0.005	0.02	0.04
P_{aCO_2}	−0.449	2.02	4.04
P_{aO_2}	−1.88	10.9	21.8

Small, but statistically significant differences were observed between the 2 instruments for pH ($p = 0.015$) and P_{aCO_2} ($p = 0.017$) for the combined data from both hospitals. There was no significant difference for P_{aO_2} ($p = 0.062$). There were significant correlations between values obtained with the i-STAT when compared to the Corning 278 for pH ($r = 0.9392$; $p < 0.001$), P_{aCO_2} ($r = 0.9804$, $p < 0.001$), and P_{aO_2} ($r = 0.9904$, $p < 0.001$). When the data from each hospital were analyzed

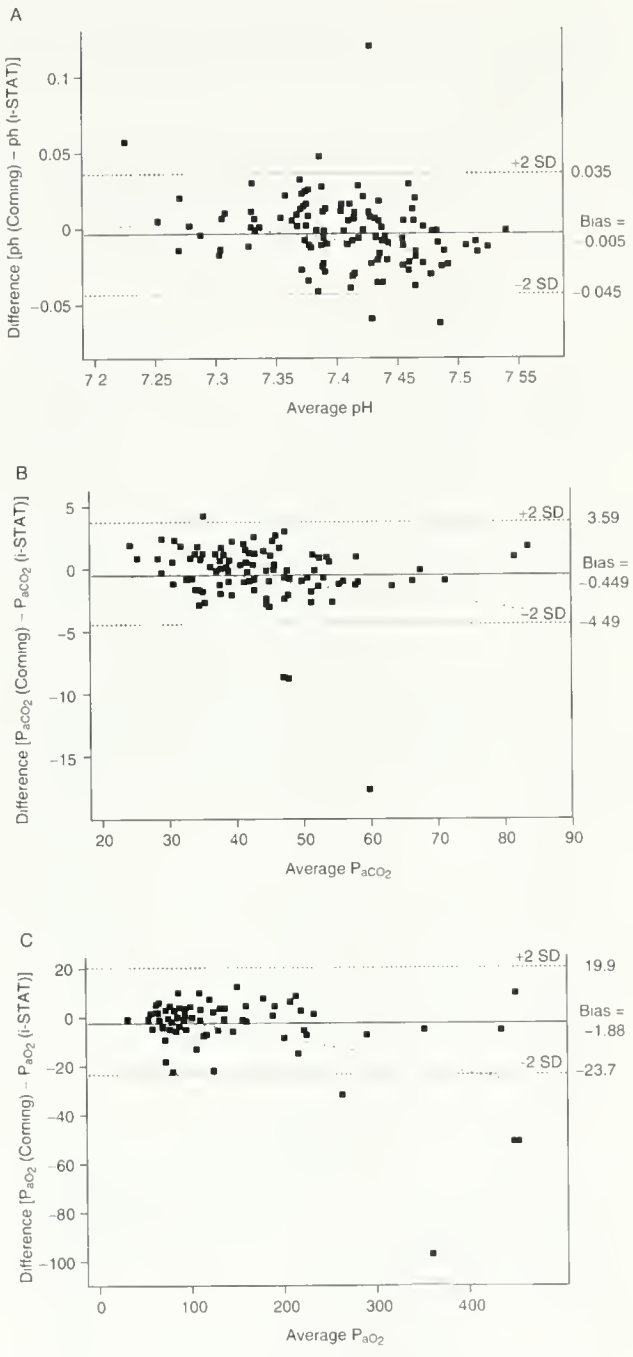

Fig. 2. Bias and imprecision for A. pH, B. P_{CO_2}, and C. P_{aO_2} (n = 119) for the i-STAT system compared to the Corning 278. —— bias, – – – ±2SD

separately, results from Hospital A (n = 70), showed small, but statistically significant differences between the 2 instruments for pH (p = 0.02), P_{aCO_2} (p = 0.03), and P_{aO_2} (p = 0.04). No significant differences (p > 0.05) were seen between results for pH, P_{aCO_2}, or P_{aO_2} from the 2 instruments at Hospital B (n = 49).

Discussion

The i-STAT system results for the combined data correlated well with those obtained using the conventional Corning 278 blood gas analyzer with r values ranging from 0.94 to 0.99 (p < 0.001). Mean values for pH, P_{aCO_2}, and P_{aO_2} were also close between the 2 systems. The slopes of the regression equations were nearly 1.0 for pH, P_{aCO_2}, and P_{aO_2}; and the intercepts were close to zero for pH and P_{aCO_2}. Although there were statistically significant differences between the 2 systems for the mean values obtained for pH and P_{aCO_2}, these differences were ≤ 0.005 units for pH and < 1 torr for P_{aCO_2}, which would be of no clinical importance. As noted above, for the combined data, there was no significant difference in P_{aO_2} (p = 0.06) between the i-STAT system and Corning 278. It is of interest to note that when the data were analyzed by hospital, there were significant differences between the i-STAT system and the Corning 278 for pH (p = 0.024), P_{aCO_2} (p = 0.028), and P_{aO_2} (p = 0.042) for Hospital A (n = 70). There were no significant differences (p > 0.05) in pH, P_{aCO_2}, or P_{aO_2} between the 2 systems for Hospital B (n = 49). The samples were collected and analyzed over a 2-month period at Hospital A, while at Hospital B all samples were analyzed during a 1-week test period. The longer testing interval at Hospital A may have introduced some variation in technique, thus increasing the probability of error.

Bland and Altman have suggested that when the range encompassed by the mean (±2 SD) of observed differences on paired measurements between a new measurement technique and an established one is not clinically important, the new analyzer can be used in place of the standard analyzer.[4,18] Bias and imprecision can be estimated by the mean difference and the standard deviation of the differences (Table 2).[16,18] The limits of agreement may then be determined by calculating the range encompassed by the mean difference ±2 SD.[18] For our study, the resulting limits of agreement for pH for the combined data would be –0.045 to +0.035 pH units and –4.49 to +3.59 torr for P_{CO_2}; both limits of agreement being of little clinical importance. However, for P_{O_2}, the range for the combined data would be –23.7 to +19.9 torr, which could be clinically important. Examination of the individual paired data points for P_{aO_2} revealed that differences of more than 15 torr between the 2 instruments occurred with 6 of the samples. Of these, 4 samples involved a P_{aO_2} > 100 torr, and 3 involved samples with a P_{aO_2} of > 200 torr. Because the i-STAT system uses a 1-point calibration only, results from samples containing high oxygen tensions may be less accurate. We are unable to account for the observed differences based on sample handling or analysis.

MacIntyre et al[4] employed a modification of the technique recommended by Bland and Altman for establishing whether the results of accuracy and precision comparisons between two blood gas instruments are "sufficiently good to justify the use of one instrument in place of another." Specifically,

MacIntyre et al have suggested that the Bland-Altman criteria be evaluated in light of the current Medicare CLIA (Clinical Laboratory Improvement Act) proficiency standards for arterial blood gases.[4] CLIA standards require that 80% of samples used for proficiency testing be within ±0.04 units for pH, ±5 torr or 8% for P_{aCO_2}, and ±3 SD of a P_{O_2} target.[19] In comparing two blood gas instruments, McIntyre et al suggested that an acceptable target range for P_{O_2} differences might be ±15.51 torr.[4] Based on these criteria, we identified that 111 of the 119 pH values (93%) obtained using the i-STAT system were within ±0.04 pH units of the value obtained with the Corning 278; 118 of 119 P_{aCO_2} values (99%) were within ±5 torr and 113 of 119 P_{aO_2} values (95%) were within ±15.51 torr, well within the CLIA requirements. In terms of bias, the i-STAT system performed as well as similar point-of-care systems,[7,20] and our results were comparable to those found in evaluating intra-arterial blood gas monitoring devices.[21,22] We recommend further study to determine the ease of use, precision, efficiency, and costs associated with the i-STAT system when compared to a conventional blood gas analyzer.

Conclusions

Arterial blood gas results obtained via the i-STAT system correlated well with results obtained with the Corning 278. There were small, but statistically significant differences between the two instruments on pH and P_{aCO_2}; however, these differences are probably not clinically important. Based on these results, we believe that the i-STAT system can be used as an acceptable alternative for the analysis of pH, P_{aCO_2}, and P_{aO_2}.

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Comparison of Accuracy and Signal Consistency of Two Reusable Pulse Oximeter Probes in Critically Ill Children

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BACKGROUND: To control costs, our institution changed from disposable (DP) to reusable pulse oximeter probes (RP). Anecdotal experience suggested that RPs are not as reliable as DPs. We compared the accuracy and signal consistency of 2 Nellcor RPs in critically ill children, with a subsequent comparison to DPs historical data. We hypothesized no difference in accuracy, a lesser signal consistency in one RP over the other, and that both RPs would be less accurate in blacks than whites. MATERIALS & METHODS: Children with indwelling arterial catheters and continuous pulse oximetry were prospectively enrolled. Nellcor Oxiband® (OB) and Dura-Y® (DY) RPs were placed on the same extremity alternating between adhesive and Velcro®-wrap attachment devices. Two CO-oximetry measured saturations (S_{aO_2}) were obtained for each subject. Oxygen saturation by pulse oximetry (S_{pO_2}) and heart rate were continuously monitored for 12 hours, and data were exported to provide a graphic display of each alarm-limit and desaturation event. Number of artifactual events was determined by examining the pulse amplitude signal during each event. A Wilcoxon signed rank test assessed significance of the difference. Bias ± precision evaluated accuracy of both probes relative to S_{aO_2}, and a paired Student's *t* test compared probes within different ranges of S_{aO_2}. Repeated measures ANOVA compared probe accuracy with respect to race. RESULTS: 100 arterial blood gas samples were obtained from 50 patients, 15 of whom were black. At S_{aO_2}s ≥ 80%, both probes performed similarly with a bias ± precision of 1.41 (2.59) for OB and 1.15 (2.58) for DY (p = 0.311). At S_{aO_2}s < 80% S_{aO_2}, bias precision for OB was 1.36 (5.19) and for DY 4.11 (3.51), p = 0.313. Both probes were less precise at S_{aO_2} < 80% compared to higher ranges. No significant difference in bias according to race (p = 0.549) was determined. Signal consistency data were obtained from 27 subjects, and no difference was found between probes (p = 0.194). CONCLUSIONS: OB and DY RPs demonstrated accuracy similar to each other and to historical data for DPs when S_{aO_2} was ≥ 80%. Signal consistency was similar. Contrary to previous studies, no difference in accuracy between black and white subjects was found. RPs are reliable in critically ill children and represent potential for substantial cost savings. [Respir Care 1997;42(7):698-704]

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Introduction & Background

Due to its enormous popularity as a noninvasive, continuous respiratory monitor, pulse oximetry is routinely used with surgical and hospitalized patients. A marked financial burden has accompanied this liberalized use of pulse oximetry. Conservative estimates place total annual pulse oximetry costs for U.S. hospitals at greater than half a billion dollars.[1] Our institution alone spent nearly $300,000 in 1 fiscal year (1993-1994) for all equipment costs related to pulse oximetry. Despite

this widespread use, few studies have examined the cost-effectiveness of pulse oximetry within critical care settings.[2,3] Therefore, the Technology Assessment Task Force of the Society of Critical Care Medicine has stated that, assuming equal efficacy of devices, the current issue is to find the most economical way to achieve continuous monitoring of oxygen saturation.[3]

Hoping to achieve pulse oximetry more economically, our institution (a large, academic, tertiary care children's hospital) changed from disposable to reusable pulse oximeter probes.* Although reusable pulse oximeter probes are readily available, convenient, and have the potential to reduce costs,[4] our anecdotal experience suggested that they were not as reliable as disposable probes. Other authors, as well, have questioned the reliability of reusable probes.[5-7] Therefore, in this study we sought to evaluate the accuracy and signal consistency of the Nellcor Oxiband® (OB) and Dura-Y® (DY) reusable probes in a population of critically ill children with a subsequent subjective comparison to disposable probe historical data. We hypothesized that no difference in accuracy would be found between the 2 reusable probes, but that the DY would demonstrate a lesser signal consistency. Because dark skin pigmentation has been shown to adversely affect the accuracy of pulse oximetry,[8] we also hypothesized that both reusable probes would be less accurate in black subjects compared to white subjects.

Materials & Methods

Subjects

The research protocol and informed consent form were approved by the University of Arkansas for Medical Sciences Institutional Review Board. Patients with an indwelling arterial catheter and a continuous pulse oximeter, who were located in either the Pediatric or Cardiovascular Intensive Care Units (ICU) at Arkansas Children's Hospital were consecutively enrolled after informed consent had been obtained. Subjects with a factor known to affect the accuracy of pulse oximetry, such as sickle cell anemia,[9,10] carboxyhemoglobin level > 3%,[11] or methemoglobin level > 3%[12] were excluded.

A total of 50 subjects was studied. Of the 50 subjects, 15 were black, and 27 were girls. The median age (range) of the subjects was 26 (0.25-360) months and median weight (range) was 10.8 (2.7-81.0) kg.

Description of Devices

The 2 reusable probes and probe-attachment devices are shown in Figure 1. Both probes are multisite oxygen transducers indicated for continuous noninvasive oxygen saturation (S_{pO_2}) monitoring. The OB probe, an adult/neonatal probe, is recommended for use in patients weighing < 3 kg or > 40 kg[13] while the DY probe is recommended for patients > 1 kg.[14] The probes were attached using either disposable adhesive wraps or soft foam wraps with Velcro® fasteners.

Fig. 1. Nellcor reusable pulse oximeter probes and probe attachment devices (clockwise from upper left corner): Oxiband® probe, Dura-Y® probe, Posey Velcro wrap, and Nellcor adhesive wrap.

Probe Accuracy

An OB and a DY reusable probe, each attached to a separate pulse oximeter, were simultaneously placed on the same region of the same extremity of each patient (ie, separate digits of the same extremity) thus minimizing any differences in perfusion. The fingers, toes, palms, and soles were all used as sites for probe attachment during the course of the study. Each probe was individually attached using the same type wrap, alternating between adhesive and Velcro wraps between subjects. Multiple OB and DY probes were used throughout the study.

Two arterial blood gas (ABG) samples for analysis by CO-oximeter were obtained from each patient. ABG samples were drawn on a schedule dictated by routine clinical management. The probes typically had been in place > 1 hour when the ABG samples were obtained. The measured oxygen saturations (S_{aO_2}) were determined with the same 7-wavelength CO-oximeter throughout the study. The CO-oximeter was calibrated daily and was verified relative to 3 different pH ranges every 8 hours. The S_{pO_2} for each probe was recorded as each ABG sample was drawn and close agreement between the pulse oximeter pulse rate and the electrocardiographic monitor pulse rate was assured.

Probe Signal Consistency

S_{pO_2} was continuously monitored for 12 hours with both probes remaining on the same extremity. We allowed the probes

*Suppliers of commercial products are listed in the Product Sources section at the end of the text.

to be repositioned every 4 hours according to ICU policy. The exact time of repositioning was recorded on a patient log to allow for subtraction from the final number of total events. An event was defined as a change in the S_{pO_2} or heart rate above or below a preset alarm limit or loss of the pulse amplitude signal. Each pulse oximeter stores 12 hours of continuous S_{pO_2}, heart rate, and pulse amplitude data. These data were then exported to a printer that provided a graphic display of each individual event. Each individual event was examined to separate artifactual events from true events. An event was considered to be artifactual if the pulse amplitude signal varied by more than 40%.[15] If an artifactual event lasted > 1 minute, each additional minute was counted as another artifactual event. True events were assumed to represent an actual change in the patient's heart rate or S_{pO_2}, whereas artifactual events suggested motion artifact or loss of the pulse signal. Loss of power to the pulse oximeter and probe repositioning were considered true events. Only artifactual events were included in the statistical analysis.

Statistical Analysis

Biologic and demographic data are presented as median with range in parentheses. Bias and precision, as defined by Altman and Bland,[16] were used to analyze the S_{pO_2} data of the 2 reusable probes. In general, bias indicates the accuracy of a measurement whereas precision implies the reproducibility of the measurement. Specific to this study, bias represents the mean of the differences between S_{pO_2} and measured S_{aO_2}, and precision is the standard deviation (SD) of the differences. A paired Student's *t* test was used to compare the accuracy of the 2 probes within specific ranges, and an F-test for equal variance was used to compare the precision between different ranges of S_{aO_2}.

A 2-factor repeated measures analysis of variance (ANOVA) was used to evaluate the effect of race and probe-attachment device (Velcro or adhesive wrap) on the accuracy of each reusable probe.

The Wilcoxon signed rank test was used to detect the presence or absence of a significant difference in artifactual events between the 2 reusable probes ($\alpha = 0.05$, $\beta = 0.05$, with 95% power to detect a 100% greater number of artifactual events for the OB versus the DY). The significant value for α was defined as 0.05. A Wilcoxon 2-sample rank sum test was used to evaluate the effect of probe attachment device on the number of artifactual events for each probe.

Results

Probe Accuracy

A total of 100 CO-oximeter ABG samples was drawn from the 50 subjects. The median (range) S_{pO_2} for the OB probes was 93 (58-100)% and for the DY probes 93 (65-100)%. Bias and precision (± 1 SD) for different ranges of S_{aO_2} are shown in Table 1. Both reusable probes have comparable bias and precision overall. The bias and precision over the 80-100% range were also similar for both probes. Below 80% S_{aO_2}, the DY tended to have a more positive bias than the OB probe. However, no significant difference between the two probes within this range was found (p = 0.313).

Table 1. Bias ± Precision (1 SD) Comparison of 2 Reusable Probes within Different S_{aO_2} Ranges.

S_{aO_2} Range	n	Oxiband®	Dura-Y®	p value
All	100	1.41 (3.11)	1.63 (2.94)	0.605
80-100%	84	1.41 (2.59)	1.15 (2.58)	0.311
90-100%	66	1.33 (2.42)	1.09 (2.34)	0.429
80-90%	19	1.79 (3.12)	1.37 (3.29)	0.654
< 80%	16	1.36 (5.19)	4.11 (3.51)	0.313

The precision of both reusable probes lessened in the range of 80-90%, although this trend did not reach statistical significance compared to the data in the 90 - 100% range (p = 0.38). The precision of each probe lessened with S_{aO_2} < 80% compared to higher saturation ranges. The p value for the OB probes was < 0.01 and for the DY probes < 0.001, comparing precision within the < 80% S_{aO_2} to the ≥ 80% S_{aO_2} range for each probe.

Table 2 compares bias and precision data for each probe between white and black subjects within the S_{aO_2} range of 80-100%. No difference in bias was detected between white and black subjects overall (p = 0.549) or with respect to probe type (p = 0.344). Also, the type of probe attachment device did not significantly affect the accuracy of the OB (p = 0.557) or the DY (p = 0.095) probes.

Table 2. Bias ± Precision (1 SD) according to Race for Each Reusable Probe in the S_{aO_2} Range of 80-100%.

Subjects	n	Oxiband®	Dura-Y®
White	70	1.45 (2.69)	1.21 (2.60)
Black	30	1.35 (2.44)	1.05 (2.59)

Probe Signal Consistency

Signal consistency data were obtained from 27 subjects. The median (range) number of artifactual events in a 12-hour period for the OB probes was 12 (0-52) and for DY probes 21 (2-50), with p = 0.194). In 14 of 27 subjects, the OB probe had more artifactual events than the DY. The reverse was true for the remaining 13 of 27 subjects. Also, no significant difference in the number of artifactual events was found between Velcro and adhesive wraps for either probe (OB p = 0.845; DY p = 0.525).

Discussion

This clinical study evaluated the accuracy and signal consistency of 2 Nellcor reusable pulse oximetry probes in a population of critically ill children. Our results indicate there was no difference in accuracy or signal consistency between the Nellcor OB and DY reusable probes when S_{aO_2} was ≥ 80%. The accuracy of both probes was comparable to that reported in the literature for disposable probes,[17-21] as well. Contrary to previous studies, no difference in probe accuracy was found relative to skin pigmentation. Exclusive use of reusable probes in pediatric patients is unique, because to our knowledge most children's hospitals are primarily using disposable probes at present.

Pulse Oximetry

Although pulse oximeters outwardly appear to be simple devices, pulse oximetry represents a significant technologic advance that uses the principles of plethysmography and spectrophotometry to provide a noninvasive measure of oxygen saturation. Several excellent reviews[19,22-24] discuss the principles behind pulse oximetry in detail, so we provide only a brief discussion here. The probe consists of a light source that transmits light at 2 different wavelengths through a pulsatile vascular bed to a photodetector. The ratio of peak and trough absorbencies at the different wavelengths correlates with the proportion of oxygenated to deoxygenated hemoglobin in pulsatile blood. A calibration curve inherent to the specific oximeter is then used to convert the absorbency ratio to functional oxygen saturation. The calibration curves were developed through data collected from healthy adult subjects, which limits the accuracy of pulse oximetry because data must be extrapolated at low S_{aO_2} ranges. Manufacturers, such as Nellcor, have modified their software, and now claim to have a precision of ± 2% within the S_{aO_2} range of 70-100% regardless of probe type.[25] However, a number of studies have shown poor accuracy below 80% (disposable and reusable probes) in critically ill children and in children with cyanotic congenital heart disease.[17-21,26] Therefore, it seems that the accuracy of pulse oximetry at low oxygen saturations may vary depending on the clinical situation in which it is applied.

Reusable vs Disposable Probes

Disposable probes have probably been the most popular type of probe used, particularly among pediatric centers. With the current emphasis on cost containment, less expensive alternatives are receiving more attention. A few of these alternatives include the use of a protective plastic shield to prolong the life of laminated disposable probes,[27,28] modification of disposable probes using adhesive supplies,[29] and, simply, reusing disposable probes. Reusing disposable probes has been shown to introduce additional error into S_{pO_2} measurement due to partial obstruction of the optical components by the adhesive backing of the probe[30] and thus may compromise patient care. A protective plastic shield does not affect disposable probe accuracy,[27,28] but its use has not been specifically addressed in the pediatric population where its application might be more cumbersome and result in inferior skin contact.

Reusable probes represent another cost savings alternative to disposable probes. Various types of reusable probes are available, some of which have been studied previously. Several different types of reusable probes were evaluated in an extensive study by the Emergency Care Research Institute in which 13 different brands of pulse oximeters were tested.[31] All accuracy data in this study were obtained using reusable clip-on probes, and each brand met the authors' expectations of ± 3% precision for S_{aO_2} ≥ 80%. In 2 other reports,[32,33] reusable clip-on probes were shown to have accuracy similar to disposable probes. However, both authors noted that clip-on probes were not designed to be attached for extended lengths of time, limiting the usefulness of clip-on probes in a critical care setting. Ohmeda (Ohmeda, Boulder CO) reusable probes have been included in several studies.[6,18,34-36] Of these studies performed in critical care settings, 2 studies questioned the reliability of reusable probes. Both Barrington et al[34] and Russell and Helms[6] found the Ohmeda reusable probe to have worse bias and to be considerably more sensitive to motion artifact than were Nellcor disposable probes, in neonatal and pediatric ICU patients.

Nellcor reusable probes, however, have only been mentioned specifically in a few studies. Jubran and Tobin[8] pooled data from Nellcor disposable and reusable probes in 54 adult ICU patients. The authors commented that 20% of the Nellcor readings had a bias of > 4%. It is not known whether reusable probes could have contributed to this variability. Although we found no reference to the Nellcor DY probe in the literature, Howell and colleagues[37] studied a modified Nellcor OB probe in children undergoing elective plastic surgery. The OB probe was secured to a plastic syringe barrel with adhesive tape and slipped onto a finger so that the probe itself made no skin contact. The modified OB differed from a Nellcor clip-on probe by a mean of −1.6%, but measured oxygen saturations were not obtained. The authors also stated this technique might not yield accurate results in the awake child, due to movement. Therefore, the newer generation of Nellcor reusable probes (OB and DY) have not been extensively studied. Because of our concerns stemming from anecdotal reports and the fact that pulse oximetry reliability varies with manufacturer and probe type, we performed this study to assure that a cost-containment measure was not done at the expense of patient care quality.

Probe Accuracy

Both of the reusable probes included in this study performed similarly over a broad range of oxygen saturations. In fact,

no significant difference was found between the two probes within any saturation range. Compared to higher saturation ranges, both probes were less precise below 90%, and particularly below 80%. This latter finding was not unexpected due to the inherent limitations of pulse oximetry at low oxygen saturations.

As mentioned previously, Nellcor Inc claims the N-200 pulse oximeter has a precision of ± 2% in the S_{aO_2} range of 70-100%, regardless of probe type.[25] Our results indicate that reusable probes achieved this level of accuracy only when S_{aO_2} was > 90%. In the S_{aO_2} range of 80 to 90%, the imprecision of both reusable probes exceeded ± 3%, and below 80% the probes were even less precise.

Although the accuracy of reusable probes differed from the manufacturer's claim, their accuracy is comparable to values reported in the literature for disposable probes. In a study of 56 children with cyanotic congenital heart disease, Schmitt et al found the Nellcor N-100 pulse oximeter used with a disposable probe had a bias ± precision of 1.9 (2.7)% in the saturation range of 80 to 90% and 5.8 (4.8)% at < 80%. Likewise, Russell and Helms[6] and Ridley[20] investigated the accuracy of pulse oximetry with disposable probes in critically ill children. They also achieved results similar to the present study, with overall bias and precision values of –0.8 (3.23)%[6] and –0.7 (3.1)%.[20] In addition, both authors stated that the accuracy of pulse oximetry worsened with S_{aO_2} < 90%, which is in agreement with our results. Similar investigations by Boxer et al,[17] Fanconi,[26] Jubran and Tobin,[8] and Lebecque et al[18] further verify the inaccuracy of disposable probes at low S_{aO_2} values. Therefore, the accuracy of both reusable probes appears comparable to the historical data available for disposable probes.

Effect of Skin Pigmentation on Probe Accuracy

Jubran and Tobin[8] reported a significant difference in pulse oximetry accuracy between subjects with black skin and those with lighter skin and recommended that a higher S_{pO_2} be used for oxygen titration in blacks. Emery[38] and Cahan et al[39] likewise have indicated that skin pigmentation may affect oximetry accuracy. Therefore, any pulse oximetry validation study should include accuracy data relative to skin color. Our results differ from what has been previously reported in that neither probe demonstrated a difference in bias or precision between white and black subjects relative to measured oxygen saturation. This difference may be secondary to the smaller number of black patients in our study: 15 compared to 29 black subjects in the study by Jubran and Tobin.[8] However, it is not known whether that study excluded patients with sickle cell disease, a disease that can adversely affect S_{pO_2} accuracy.[9,10] Alternatively, pediatric patients may not be as heavily pigmented thus lessening the effect on pulse oximetry. Further investigation is needed to conclusively resolve this issue.

Signal Consistency

Signal consistency was evaluated in this study because our anecdotal experience suggested the reusable probes were more sensitive to movement artifact, resulting in a large number of false alarms. Prior to comparison of the 2 probes, we arbitrarily specified that the OB would have to produce twice as many false alarms as the DY in order to justify clinical use of the more expensive DY. No significant difference in signal consistency was found, and the type of wrap did not affect the consistency of either probe. However, a direct comparison between disposable and reusable probes is needed because no signal consistency data are available for disposable probes. Given that both reusable probes in our study had similar accuracy and consistency, our institution primarily uses the less expensive OB.

Financial Implications

In 1994, our institution began using reusable probes exclusively in all inpatients and outpatients. Disposable probes were used only in the operating rooms, recovery rooms, and by our transport teams. Following the first fiscal year in which reusable probes were used, actual annual costs for all equipment related to pulse oximetry (not including the cost of cleaning and disinfecting reusable probes) reported on a budget sub-account decreased from $297,000 to $65,000 representing a savings of $232,000. This substantial savings was achieved entirely by reducing expenditures for disposable probes. However, cost savings could be offset if additional ABG analyses were needed because of reusable probe use. Bierman et al[2] showed that pulse oximetry significantly reduced the number of ABG analyses needed in the postoperative care of cardiac surgical patients, but it is unknown whether the use of reusable probes would adversely affect this result. Also, if probe age were found to adversely affect accuracy, more frequent probe replacement would also reduce potential cost savings. A cost-effectiveness study directly comparing disposable to reusable probes is needed to answer these questions.

Limitations

In this study, we compared 2 reusable pulse oximetry probes. It is not known whether reusable probes become less accurate with repeated use. We did not control for probe age or quality and, therefore, this could have potentially influenced our results. However, because our data are comparable to the data of previous studies using disposable probes, we speculate that probe age is not a significant factor. Additionally, although the OB probe is recommended by the manufacturer for use only in patients weighing < 3 kg or > 40 kg, we applied both probes to all subjects regardless of weight. Because no significant differences were observed between the 2 probes and each subject served as his own control, we do not believe

that use of the OB probe outside of the recommended weight range adversely influenced our results. This study was also limited in that 2 different probe-attachment devices were used. No trends in bias or precision related to the probe attachment device were found, however. One other limitation of this study was that we did not make a direct comparison with disposable probes. A wealth of reference data for disposable probes exists in the literature so we believe our subjective comparison was reasonable to perform.

Conclusions

The OB and DY reusable pulse oximetry probes demonstrate accuracy similar to each other and to historical data for disposable probes. Signal consistency is similar for both reusable probes, as well. Confirmatory ABG analysis may be needed in hypoxemic patients, but this should not represent a change from current practice with disposable probes. The finding of no difference in accuracy for either probe relative to skin pigmentation is surprising and warrants further investigation. We believe that reusable probes are reliable in critically ill children and represent potential for substantial cost savings.

PRODUCT SOURCES

Pulse Oximeter:
Model N-200, Nellcor Inc, Pleasanton CA

Pulse Oximeter Probes:
Oxiband® Model Oxi-A/N, cost $125/probe (as of November 1, 1996), Nellcor Inc, Pleasanton CA
Dura-Y® Model DY-S, cost $275/probe (as of November 1, 1996), Nellcor Inc, Pleasanton CA

Probe Attachment Devices:
Pediatric/Infant Adhesive Sensor Wrap, Model P/I, Nellcor Inc, Pleasanton CA
Adult/Neonatal Adhesive Sensor Wrap, Model ADH-A/N, Nellcor Inc, Pleasanton CA
Velcro® Pulse Oximeter Probe Wrap, Model # 6554, Posey Co, Arcadia CA

CO-Oximeter:
Model 2500B, Ciba Corning Diagnostics Corp, Medfield MA

Printer:
ThinkJet, Hewlett-Packard Co, Waltham MA

ACKNOWLEDGMENTS

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Books, Films, Tapes, & Software

Practical Math for Respiratory Care: A Text and Workbook, by R Sibberson. Softcover, 291 pages. St Louis: Mosby—Year Book Inc, 1996. $18.95.

Because respiratory care is highly technologic, its advanced practice requires the understanding and implementation of many mathematical concepts and equations. **Practical Math for Respiratory Care** is an excellent workbook for respiratory care students. In this text, Sibberson clearly presents mathematical formulae commonly used in respiratory care and explains their clinical importance. Practice exercises in each chapter assist the reader in developing proficiency. This workbook is easy to read and can be used for self-instruction by any motivated reader.

The first chapter reviews the metric system with the conversion of liters to milliliters and grams to milligrams. Chapter 2 explains how to calculate the density of a gas. A comparison of air to heliox clearly demonstrates the effect of density on a patient's work of breathing. For example, the density of air is 1.3 g/L, and the density of heliox is 0.43 g/L. Because heliox is only one third as dense as air, it is easier for a patient in respiratory distress to breathe heliox.

A review of the gas laws is followed by the mathematics used to calculate the content and duration of gas cylinders and liquid oxygen reservoirs. The title of Chapter 4 is Flowrates. This chapter covers the calculations used to determine a patient's inspiratory flow and the calculations used to determine the flow of air-entrainment devices. Chapters 4 and 5 present the same concepts of flow and the mixing of gases. The explanation of estimating a patient's inspiratory flow is well done but could have been more complete had the author included the normal inspiratory flow pattern to explain the limitations of the equations. Nonetheless, the chapters clearly prove that setting up an air-entrainment mask (Venturi) according to the manufacturer's recommendations is not always appropriate. When the patient's inspiratory flow exceeds the device flow, the patient draws in room air and does not receive the prescribed oxygen concentration.

Chapter 5 repeats the equations used in Chapter 4. The equations that compute air/oxygen ratios focus on oxygen concentrations instead of flowrate in this chapter.

How does one convert a medication available as a percent or a dilution to mg/mL? Chapter 6 shows how. This may be an important chapter for many respiratory care practitioners who are accustomed to using only unit dose medications.

Equations used to express humidity are followed by the math used to predict the P_{aO_2} with a change in oxygen concentration, the oxygen content of blood, the alveolar air equation, and the lung volumes and capacities.

In Chapter 12, Mechanical Ventilation, a typographical error on Page 139 confuses mL/lb with mL/kg. All of the ensuing equations use this incorrect formula and cause erroneous answers.

The correct calculations for different types of patient dead space precede cardiac output, shunt determination, oxygen delivery, and hemodynamics. All of these topics are followed by ample practice exercises that almost guarantee mastery of the concepts upon completion.

All the concepts and subjects in **Practical Math for Respiratory Care** should be a part of every respiratory care student's education. This textbook provides an excellent tool to master these concepts.

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Home Mechanical Ventilation. D Robert, B Make, P Leger, A Goldberg, J Paulus, T Willig. Softcover, 343 pages. Paris, France: Arnette Blackwell SA, 1995. $65.

Home Mechanical Ventilation is a collection of works by some of the most well-known experts in the field of home mechanical ventilation. This book, containing a review of the Fourth Annual International Conference on Home Mechanical Ventilation held in Lyon, France in 1993, is a complete reference for any medical professional interested in assisted ventilation.

The authors cover a variety of topics, including sensitive areas such as withholding and withdrawing mechanical ventilation. The book is divided into 5 sections: Organization and Ethics of Home Ventilation; Methods and Techniques of Long-Term Home Ventilation; Pathophysiology of Long-Term Home Mechanical Ventilation; Chronic Respiratory Insufficiency; Use of Continuous Positive Airway Pressure in Sleep Apnea Syndrome; and Outcomes and Indications for Long-Term Home Ventilation. The book covers most areas of mechanical ventilation in the home.

In the first chapter, Dr Goldberg reviews the impact of high technology home care and health care reform. High technology home ventilation represents a highly complex system that requires interaction and coordination to succeed. In the United States, the care of ventilator-assisted individuals is fragmented, leading to inefficiencies and increased expenses. In Chapter 2, Dr Make reviews the guidelines for withholding and withdrawing mechanical ventilation and the concept of ethical principles. With advances in medical therapies, particularly those which increase survival rates, policies regarding withdrawing and withholding life support are essential. Institutions must have policies and procedures to guide and protect all parties. He supports his statements with The American Thoracic Society's Statement on Withholding and Withdrawing Life Sustaining Therapy.

The second section, Methods and Techniques of Mechanical Ventilation, is complete with drawings and explanations of the components of ventilators. Dr Kacmarek compares intensive care ventilators to home care ventilators in precise detail. The concept of volume-targeted versus pressure-targeted ventilation is thoroughly explained. The author also provides a diverse list of internationally available home ventilators. The importance of mechanical work of breathing is also well presented. The history and application of negative pressure ventilation and nasal ventilation are also explained. Secretion clearance is reviewed in this section by Gross.

The sections covering Pathophysiology, Long-Term Home Ventilation, and Chronic Respiratory Insufficiency include information on sleep and noninvasive monitoring of CO_2 during sleep, complete with tables and graphs

documenting that P_{ETCO_2} inadequately reflects P_{aCO_2} particularly in the presence of supplemental O_2 or with bi-level positive airway pressure ventilation. The review of REM (or rapid eye movement) versus non-REM sleep by Levy and Pepin includes tables, examples, explanations, and comparisons of normal and abnormal sleep study recordings.

Dr Make reviews the transition and indications for long-term mechanical ventilation in a complete chapter that covers everything from sites for long-term care to quality of care issues. The author provides useful tables for clinical and physiologic stability. He covers the 6 phases of rehabilitation for home ventilator-assisted individuals—stabilization, evaluation, discharge planning, home care, and follow up.

The last few chapters address the issues specific to different disease entities that may require home ventilator assistance including cystic fibrosis, Duchenne muscular dystrophy, congenital central hypoventilation, and amyotrophic lateral sclerosis.

The illustrations and tables of information lend credibility to this volume. The photographs and roentgenograms also illustrate the authors' points. I did notice two typographical errors in the book on Page 4 and Page 169.

I recommend this book to any medical professional who is in any way involved with home mechanical ventilation. This is not merely a "how-to" book with descriptions and illustrations of the components of home ventilators, but rather it is a thought-provoking book that touches upon all aspects of ventilation, from the social and economic impact to the physiology and components of mechanical ventilators. This book would be a welcome addition to any medical library.

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Letters

Confusion over Mechanical Ventilation Terminology

I commend Mr Nilsestuen and Mr Hargett on their overview of the graphic analysis of pressure, volume, and flow during mechanical ventilation.[1] I believe that the monitoring and interpretation of scalars and loops are skills that all critical care respiratory care practitioners (RCPs) should acquire in order to secure their place at the bedside of mechanically ventilated patients. In fact, it was my original intent to have each of our students review this article during our class discussions of waveform analysis.

However, as I read the article, I noted several discrepancies in the use of the phase variables "trigger" and "cycle." Although the authors correctly define the trigger phase variable on Page 1106 and discuss triggering mechanisms thoroughly on Page 1109, they use the term "cycle" synonymously with "trigger" throughout Pages 1106 and 1107. The variable (pressure or flow) that causes inspiratory flow to *begin* is usually not the same variable that causes inspiration to end. The authors make this distinction correctly when they note that the increased use of microprocessors has made most volume-targeted modes time-cycled.[1]

Chatburn has developed and published a ventilator classification system that is based on similarities among ventilators and their interaction with the respiratory system.[2] This system uses a consistent terminology that is not vague or contradictory. The Chatburn system has been widely accepted and published,[3-8] first in this journal and subsequently in many textbooks.

The Chatburn system defines the trigger variable as that variable (pressure, flow, or time) that causes inspiration to begin, once a preset value has been reached. The most common trigger variables are time and pressure. The cycle variable is that variable (pressure, flow, time, or volume), that causes inspiration to end (ie, 'cycle off').[2] The breaths delivered by an intermittent positive pressure breathing device (IPPB) are pressure-cycled. The Emerson 3MV ventilator delivers an intermittent mandatory ventilation (or IMV) breath that is volume-cycled, whereas a breath delivered during the pressure support mode is flow-cycled. These terms should not be used interchangeably.

I again applaud the Corner Editors for publishing an excellent overview of the benefits of graphic analysis in the mechanically ventilated patient. I believe that the Graphics Corner will become a valued addition to the Journal.[9] However, I encourage all educators, clinicians, and ventilator manufacturer representatives to become thoroughly familiar with the Chatburn classification system so that we can all be on the 'same page' when discussing mechanical ventilator operation.

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The Corner Editors respond:

We agree in concept with your suggestion that it would be more advantageous to use one system in discussions relating to ventilator terminology and classification; specifically to use the Chatburn classification system. We support the use of the Chatburn classification and cited it in our original article as you so note. However, our observation is that the general practitioners are slow to adopt this system.

The purpose of the original article was to establish the background for initiation of the Graphics Corner, and our philosophy was to present concepts in ways that were as reader-friendly as possible. Consistent with this philosophy, we had several discussions during the editing process over the use of terminology.

The educational task of converting from one classification system to another is a slow and sometimes arduous process that requires consistency and persistence among educators, authors, and editors. Probably the more difficult task is providing continuing education to the general practitioners in the field. Ventilator terminology includes colloquialisms and jargon that over time have been adopted regardless of their correctness—much in the manner that terms are added to the dictionary over time as a result of the general understanding and acceptance by the common user.

With regard to this process of educating the field about new classification systems, it is true that many of the new generation textbooks have adopted this system; and, thus, the crossover to new students learning the system for the first time has already been facilitated. In evaluating the field as a whole we need not forget that the majority of practitioners are no longer recent graduates. At best (and sadly) only about a third of practitioners receive the Journal and, thus, firsthand exposure to the classification system. We share a responsibility to discuss methodology in terms that

they will understand, in hopes of encouraging their participation in the learning process. Although the conversion from one classification system to another is still taking place, it would probably be helpful to practitioners to note the newer terminology, and authors, editors, and reviewers should keep this in mind. When we reread the Corner, we didn't think that the terminology leads the reader to misinterpretation, but we are also sensitive to your evaluation and will keep it in mind for future submissions.

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Graphics Corner Editors

Call for Consistency in Waveform Analysis Terminology

I read with interest the article in Graphics Corner about the patient with status asthmaticus and enjoyed the ensuing analysis of waveforms.[1] As a student of respiratory therapy, I find waveform analysis both helpful and enlightening. As I learn more about the phenomena of hyperinflation, air-trapping, and intrinsic positive end-expiratory pressure (or auto-PEEP), and the various waveforms associated with them, my understanding of respiratory anatomy, physiology, and mechanical ventilation is enriched.

I find it unfortunate and confusing, however, when words are used interchangeably that, to me, have decidedly different meanings. This is more than an obsession with semantics. I believe it would help the clarity of future discussions if we could agree upon certain conventions.

Traditionally, respiratory care deals with the variables of volume, flow, and pressure. Waveform analysis of these variables is yielding ever-increasing insights into the effects of mechanical ventilation.[2,25-30] Regardless of the cause (for example, air-trapping may be the result of insufficient expiratory time[2,44,45] and/or dynamic compression of the airways[3] or an obstructive defect[4]), it would be helpful if the words used to describe their graphic manifestations could be more uniform. I propose, perhaps, as a starting point for future discussion, that we begin by agreeing that "hyperinflation" refer to volume,[4,5] "air-trapping" refer to flow,[6] and "auto-PEEP" refer to pressure,[2,172] all as functions of time.

There is an inevitable interplay between these variables, ie, insufficient expiratory time can lead to auto-PEEP and auto-PEEP when perceived as flow may be referred to as air-trapping and either can lead to hyperinflation. But can we agree that, when discussing the waveform analysis of these variables, there be consistency of terms?

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Retrospectroscope

Premature Science and Immature Lungs
Part III. The Attack on Immature Lungs

In Part I, I gave an account of the discovery of surface forces by Laplace and by Young (1805-1806) and of its first application to the lung by Von Neergaard in 1929. Part II told some highlights of the rediscovery of surface forces, the discovery of pulmonary surfactant and of its unique properties, and the finding that the lungs of babies who died of respiratory distress syndrome ("hyaline membrane disease") lacked this remarkable substance; part II dealt largely with the work of Radford, Pattle, Clements, Avery, and Mead. Part III tells of the multidisciplinary attack on immature lungs; it concludes this series, but not the story, because, as is almost always true in science, many questions still need answers.

Introduction

Thus far, the cast of characters—from 1805 to 1959—can be counted on the fingers of two hands. From here on, it numbers hundreds, perhaps thousands. The post-1959 cast is large because many important questions had to be answered: What is surfactant? Where does it come from, where does it go and what regulates its formation and movements? Can it or a similar substance be prepared synthetically and used as replacement therapy? Can the physician, instead of nature, make an immature lung become mature? Can the physician not only maintain the life of a newly born baby until the lung matures but also ensure normal postnatal function of all organs?

Fortunately, as often happens in science, pediatricians and pulmonary scientists were ready for new fields, and study of the newly born was one of the most challenging of these. And new technics, concepts, and knowledge discovered for other purposes, or just for the sake of knowing, were ready at the proper time to rescue the baby with immature lungs; these included the modern technics of lipid and protein chemistry (e.g., differential ultracentrifugation, a large number of chromatographic methods, electrophoresis, immunological methods, and the use of radioactive isotopes), high resolution electron microscopy, cell culture, and cell biology in general, the concept of intensive care units, and the ability to examine amniotic fluid.

It would take a scholarly monograph or two to tell of the contributions from many scientists in many disciplines that made the respiratory distress syndrome one of the best studied of all disorders, and it would take most of the pages in this long article just to list those involved. All I can do is to tell of a few.

What Is Pulmonary Surfactant?

As biochemical technics became more and more powerful, knowledge of the chemical composition of surfactant became more and more exact. Macklin, who had only light microscopic and histochemical technics at his command, suggested that the surface lining of alveoli contained mucopolysaccharides and myelinogens and spoke of it as a "mucoid film" (48). Pattle in his 1955 report (49) noted that his bubbles owed their stability to an insoluble surface layer that was attacked successfully by protein-splitting enzymes such as pancreatin or trypsin. He said, "It is thus evident that the alveoli are lined with an insoluble protein layer" and "findings suggest that a layer of some form of mucus (Macklin 1954), secreted in the depths of the lung, is the source of the insoluble lining layer." In his 1958 paper (50) he suggested that the "lining layer is ... of similar thickness to a monolayer of protein spread on the surface of water, and very much thinner than any recorded membrane or anatomical structure."

Clements in his 1957 paper noted that surfactant was "saline-extractable" and "probably mucoprotein" (51). But in 1961, three groups, each using different methods, characterized it as a lipoprotein. Pattle and Thomas (52) forced water down the main bronchus of the excised lung of a cow, allowed the water to well out, laden with bubbles, washed and dried the material, and analyzed it spectrophotometrically; it had all of the characteristics of a lecithin-protein complex. Buckingham made extracts of sheep lungs, put them in a Langmuir trough, compressed the surface, and harvested

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folded films of surface material; she too found it to be a lipoprotein (53). And in the same year, Klaus, Clements, and Havel (54), using Bondurant and Miller's newly developed technic (collecting thick white foam from the trachea of beef lungs ventilated with intermittent positive pressure and perfused with saline through the pulmonary artery) (55), isolated a phospholipid fraction that decreased surface tension as much as extracts of whole lung; the material closely resembled dipalmitoyl lecithin.* The chemical analysis suggested that a matrix of protein was an essential component of functioning surfactant. A year later Brown isolated dipalmitoyl lecithin from saline washings of alveoli (56).

It is interesting that in 1946 Thannhauser and his associates (57) analyzed various organs for what was then called hydrolecithin or dipalmityl lecithin (but none other than our new friend DPL, or even newer, DPPC) and found that lung contained more of it than did other large-animal organs except brain. Thannhauser remarked that the physiological significance of the compound was unknown; I don't believe that he or anyone else ever made any attempt to find out why it was there even though Leathes in 1925 (58) had studied the behavior of hydrolecithin (DPL, DPPC) in surface films. In the 1940s, it was believed that the lung was an organ designed for gas exchange and the fewer cells there to get in the way of gas exchange the better. This is another example of premature science. Today, if someone found a new chemical substance in high (or even low) concentration in lung tissue, it would excite the interest of many scientists.

But DPL or DPPC wasn't the end of the story. King summarized present knowledge of the lipid composition of the lung in 1974 (59); his table 1 contains 14 different lipid compounds isolated from the total lipids of whole lung—some in easily separated fractions of lung and some in fractions isolated by more sophisticated technics.

What about the protein fraction of surfactant? It is now certain, by use of immunologic technics, that surfactant contains one or more *specific* apoproteins that come neither from plasma nor from bacteriological contamination of lung tissue. Their function may be to accelerate the extracellular transport of surfactant from its intracellular origin to the alveolar interface (60). Mephistopheles in Goethe's *Faust* remarked that "blood is a super extraordinary juice"; it appears that surfactant, when fully characterized, will also be a "super extraordinary juice."

But chemical characterization of the phospholipids and apoproteins in surfactant did much more than just that. It opened a whole new field of biochemistry of the lung so that by 1976 it was possible for one to read a monograph of 534 pages entitled *The Biochemical Basis of Pulmonary Function* (61). And this was not merely biochemical analysis of whole lungs put through a meat grinder but separation of lung tissue into individual cell types, attempts to produce pure *in vitro* cultures of these, and the beginnings of examining the intracellular components of each. The alveolar Type II cell is one of these and is now known to be the source of surfactant.

Where Does It Come From?

Just as the development of new and more powerful methods provided answers to the question, "What is surfactant," so the use of the electron microscope provided answers to "Where does it come from," and the answers now included not only what *cell* but what parts of what cell.

Macklin, the first to propose the existence of surfactant, pointed to what we now call the alveolar Type II cell. This cell has had a lot of names. Macklin called it first the epicyte and then the pneumonocyte and more specifically the granular pneumonocyte. Others have called it the Type B cell; the Type II pneumonocyte; the great, large, or cuboidal alveolar cell; the secretory alveolar cell; and the niche, septal, or wall cell. Pattle was sure that surfactant came from deep in the lung and noted that "there seems very little [deep] in the lung except these alveolar cells which could possibly produce the complex" (62).

In 1954, Low (63) and Schlipköter (64), pioneers in studying the lung by electron microscopy, found mitochondria in the alveolar epithelial cells and also some unusual inclusion bodies with lamellar forms Between 1956 and 1959, Schultz saw what he called mitochondrial transformations into lamellar forms, and for a while, histologists thought that at least some mitochondria turned into lamellar inclusion bodies.

The first connection between structure and function came a few years later. Woodside and Dalton (65) used the electron microscope in 1958 to study these forms in the lungs of mice and noted that they were absent until the seventeenth or eighteenth day of gestation (full term in mice is 19 to 21 days). Four years later, Buckingham and Avery (66) found that they could not detect surfactant in the lungs of fetal mice until the seventeenth or eighteenth day of gestation; the appearance of lamellar forms and surfactant at about the same time led them to propose that the lamellar forms secrete surfactant.

In the same year, Klaus and associates (67) studied structure and function (surface activity) in the same lungs and concluded that "the surface active lining of the lung develops during the process of lamellar transformation of mitochondria in the alveolar epithelial cell." Pattle (62), in his 1965 *Physiological Reviews* article, questioned whether their mitochondrial fraction was pure or whether this fraction contained a number of discrete organelles, and he placed the subcellular origin of surfactant in his list of unanswered questions.

*The term *lecithin* is gradually disappearing from textbooks of biochemistry and is being replaced by the more specific *phosphatidyl choline*. Instead of the DPL (dipalmitoyl lecithin) of the 1960s, you will now see DPPC (dipalmitoyl phosphatidyl choline). I am reminded of the Swedish scientist working in America who said rather plaintively: "Just as I learn to say jam, you change it to yelly."

In 1965 Campiche (68), fixing lung tissue with potassium permanganate (which binds to saturated lipids) rather than osmium tetroxide (which does not), believed that he could safely say that the lamellar inclusion bodies were similar to myelin figures and were composed largely of phospholipids, possibly similar to saturated lecithin, then known to have powerful surfactant properties.

But not everyone believed that the answers were all in. Some suggested that surfactant was assembled, wholly or in part, in cells that were not part of the alveolar wall; two candidates that were proposed were the Clara cells in terminal bronchioles and alveolar macrophages. Eventually, overwhelming indirect evidence and convincing direct evidence, based on developmental, cytochemical, and autoradiographic studies, pointed only to the lamellar inclusion bodies of the alveolar Type II cell as the surfactant factory and eliminated its mitochondria and other non-alveolar cells (see Gil and Reiss [69]).

But cell biologists had now committed themselves to the study of alveolar cells, and a modern cell biologist is not satisfied with a static picture of what a cell looks like at one moment (no matter how great the magnification and resolution), but wants to visualize and reconstruct dynamic events in the daily life of the cell. Surfactant, which means phospholipids and proteins, must come from somewhere within the cell, be assembled into lamellar inclusion bodies, and, when so directed, move out of the cell—through the cell membrane into the alveolar air space and by some magic become a monomolecular layer covering everything in sight.

Dr. Mary C. Williams has kindly selected from her vast collection some electron micrographs that show the birth of a lamellar inclusion body, its coming of age, and finally its leaving its home to venture out into the air spaces.

Figure 1 shows part of an alveolar Type II cell. At the top left is just a bit of the cell nucleus. In the center is a lamellar body. It bears a strong resemblance to the layers (lamellae) of an onion except for the dense center of the lamellar body. It also resembles the arrangement of long-known myelin layers, noted in 1854 by Virchow, and later shown to consist of bimolecular leaflets, or lamellae of lipids, that alternate with layers of water. Bimolecular leaflets of lipids, together with protein, are also part of the structure of cell membranes and have been studied extensively in nerve tissue. Their arrangement as intracellular inclusion bodies makes the alveolar Type II cell unique.

The beginning of a lamellar body is shown in the inset in figure 1. As described by Williams and Mason (70), synthesis of one lamellar body component, presumably protein, may precede initiation of phospholipid synthesis. The electron-dense, homogeneous appearance of the granular matrix suggests that the content is largely protein. The number of lamellae increases as the forming lamellar body enlarges, but the mechanisms by which phospholipid is added to the growing granule are not certain. Autoradiographic studies of adult lung suggest that small lamellar bodies may shuttle phospholipid from Golgi to nascent lamellar bodies. Other morphologic observations clearly demonstrate that, later in development, multivesicular bodies participate in lamellar body formation, perhaps by fusion.

What regulates the number and size of lamellar bodies is not known, although adrenal cortical hormones certainly play a role in maturing alveolar Type II cells to the stage of producing lamellar bodies. Some have evidence, not yet completely convincing, that the vagus nerves play a regulatory role.

What prompts mature lamellar bodies to seek the surface of the cell and slip through the cell wall into the air spaces

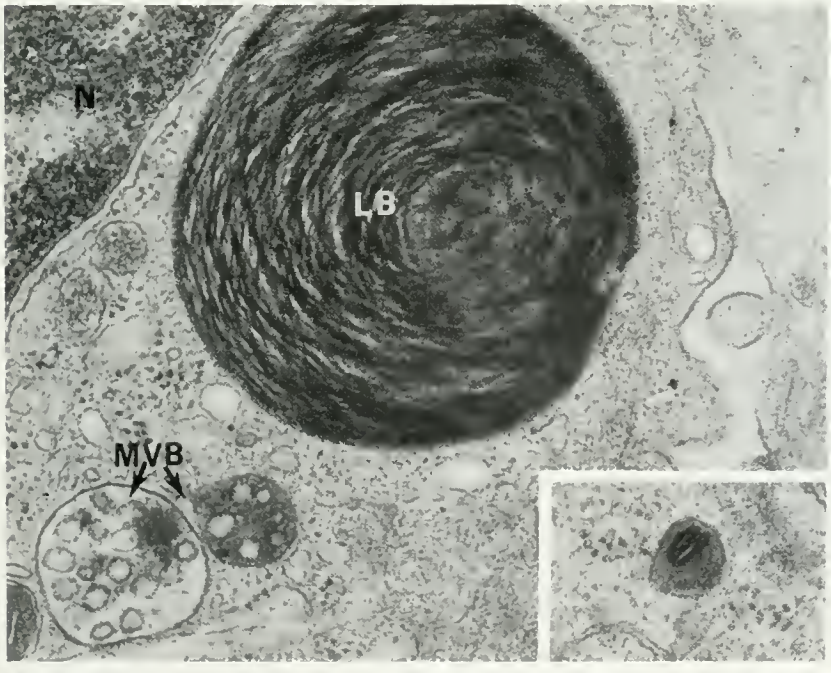

Fig. 1. Portion of an alveolar Type II cell from adult rat lung. N = nucleus. LB = large (mature?) lamellar body. MVBs = multivesicular bodies (Original magnification: × 29,000). Courtesy of Dr. Mary C. Williams. *(Inset)* Small dense granule in alveolar Type II cell of 21-day fetal rat lung. It contains acid phosphatase and a few lamellae. Such a granule is the earliest recognizable lamellar body in fetal lung; it precedes by several days the appearance of lamellae. (Original magnification: × 75,000.) Courtesy of Dr. Mary C. Williams.

(figure 2) is not known. Once there, the strands or membranes of a lamella unwind and become transformed into tubular myelin, a constant element of the extracellular lining layer of mammalian alveoli and a second form of surfactant; lamellar body membranes become continuous with those of the forming tubular myelin. If ever proof was needed that intracellular lamellar bodies become intra-alveolar lamellar bodies and these then become tubular myelin, it is provided by the continuities, shown in figure 3, between the unwinding lamellae and the threads of the tubular myelin lattice-work (71). The centers of many secreted lamellar bodies are then seen to contain acid phosphatase-reactive material.

We've come a long way in 25 years from uncertainty about the very existence of a continuous cellular lining of alveoli (were the pulmonary capillaries naked?) to proof of a cell lining covered with a noncellular lining of super extraordinary juice.

Fig. 2. Lamellar body being extruded from alveolar Type II cell into the lumen of an alveolus. 21-day fetal rat lung (Original magnification: × 35,000.) Courtesy of Dr. Mary C. Williams.

Fig. 3. Portion of a lamellar body that was extruded into a fluid-filled alveolar lumen of 21-day fetal rat lung. Note the continuities between the membranes of the lamellar body and tubular myelin (the lattice-like material on the right); these continuities suggest that a second material is formed within the alveolar lumen. Both the original and the new material are believed to be surfactants. (Original magnification: × 88,000) (From Williams [71]; reprinted by permission of publisher.)

Predicting Immature Lungs

There are many wondrous things about life. One of the most remarkable is how a single cell, the fertilized ovum, differentiates to form all of the highly specialized fluids, cells, tissues, and organs that make up a fetus, how the fetus develops into a newborn baby, how the baby grows into a pubescent child and the child matures into an adult—with each single event occurring on schedule, neither too early nor too late.

In the lungs, for example, the cuboidal cells that line what later on will be air-filled alveoli must become exquisitely thin, on schedule, to facilitate the postnatal transfer of gases between air and blood. And pulmonary capillaries, although little blood

flows through them in fetal life, must, again right on schedule, multiply in close relationship to the future air sacs and be ready to accept the entire output of the heart each minute. Further, the alveolar surfaces must become prepared so that they permit inflation during inspiration and resist collapse during expiration. An essential item is surfactant, to prevent alveolar collapse after contraction of strong inspiratory muscles has brought the first breath of air deep into the baby's lungs and the time has come for the first expiration. The most remarkable part about this process of differentiation and development is not that once in a while something is off schedule, but that it almost always goes right *on* schedule.

What is the time schedule in the human fetus for ensuring functioning surfactant? I say *functioning*, because as we have noted earlier, it can function only when it has spread as an extremely thin layer on the air side of the cells that line the alveoli. So there are really several schedules for surfactant: its synthesis; its packaging into lamellar bodies within alveolar Type II cells, its migration to the cell wall, its passage through the wall, and finally its transformation into an exceedingly thin surface layer. Total surfactant (intra- and extracellular) can be measured by mincing or homogenizing whole lung; intracellular surfactant can be estimated by counting the number of lamellar bodies (72); surface surfactant can be measured in lung washings or lung fluid, obtained without letting the insides of cells spill out.

Intracellular surfactant in the human fetal lung appears long before there is a known need for it, at about the eighteenth to twentieth week, before a fetus is viable even if a physician could ventilate the lungs. However, it cannot usually be recovered from alveolar surfaces until about the thirtieth week and now the fetus *is* viable; at about the thirty-third week, the amount on surfaces begins to increase with a rush and by the end of a normal term, it is in abundance just where it ought to be.

Knowing the time when surfactant should normally arrive at its place of business could be very useful clinically if the physician had answers to two questions: (1) Does a particular fetus, apt to become a baby prematurely (either naturally or because of medical need for early delivery), have adequate surfactant ready to go to work? (2) If it does not, can anything be done about it?

First, *prenatal* tests. Fortunately, in the 1930s obstetricians learned from a radiologist (73) and from a biochemist (74) that, particularly in the last trimester of pregnancy, it was safe to insert a needle through the pregnant mother's abdomen directly into the amniotic sac and draw off a small sample of amniotic fluid for analysis. Until the 1960s, this could not be of any diagnostic use in a fetus with immature lungs because everyone "knew" since 1885 (75) that fetal lungs were filled with fluid and that this was mostly amniotic fluid (and whatever else was in it) that somehow or other had worked its way down the trachea into the lungs along with a little mucus secreted by glands lining the airways. But some had the idea that the flow of fluid between amniotic fluid and alveoli was mainly *out* of the lungs and *into* amniotic fluid and not the other way round, and they proved their point.

Jost and Policard in 1948 (76) showed, with some experimental overkill, that the lungs of the fetal rabbit became abnormally filled with fluid even after they had decapitated the fetus and securely tied off the neck, including the trachea; they proposed that the lungs contributed fluid to the amniotic fluid rather than the other way round. Setnikar, Agostoni, and Taglietti in 1959 (77), with a more sophisticated experimental technic, delivered the head of fetal goats from the mother's uterus, tied a tube in the trachea of the fetus, replaced the fetus in the uterus, and sewed up the incision in the uterus, leaving the other end of the tube on the outside. They were still able to collect tracheal fluid, thus confirming the studies of Jost and Policard; the fluid could not possibly have come from amniotic fluid and must have originated in the lung.

In the 1960s, Forrest Adams and his associates (78) did a series of biochemical studies on lung fluid in fetal lambs that proved (1) that its chemical composition differed significantly from that of plasma or of amniotic fluid, (2) that fetal lung fluid contained surface-active materials not present in blood or pure amniotic fluid (79) (80), and (3) that the lung fluids flowed into amniotic fluid. This flow could occur either because the pressure developed by lung fluid as it formed was greater than that of amniotic fluid (81, 82) or because the fetus made breathing efforts *in utero* that brought some amniotic fluid into the lungs during inspiration and then expelled a mixture of lung fluid and amniotic fluid into the amniotic sac (83). Others showed that fetal alveolar liquid is not an ultrafiltrate of plasma but a special material formed by the fetal lung (84), and that the lung was the source of phospholipids present in tracheal fluid and probably of much of the phospholipids in amniotic fluid (81).

However, the first separation of lung fluids from amniotic fluid, without using tracheal tubes, came about in 1963, and with it came further proof that lung fluids flowed upward and outward and contained pulmonary surfactant. I have a brief report of it in my files in the form of an application, dated September 21, 1964, from a Senior Lecturer in Obstetrics at the National Women's Hospital in Auckland, New Zealand. The applicant's name was Dr. Graham Liggins (we come back to him later); he wanted to spend his sabbatical year working with Dr. Louis Holm, a physiologist at the University of California in Davis, and he needed $6,000 to help him survive our high cost of living for a year; this he received from the Lalor Foundation. Liggins's "plan of work" outlined in his application to the Lalor Foundation stated (in part):

> Using the facilities of the Animal Research Station, Ruakura, Hamilton [New Zealand], during the past three years, these techniques have been developed in the sheep.
>
> As the first step towards fetal transplantation in late pregnancy, the fetus is transferred from the uterus into a plastic bag within the maternal [sheep] abdomen, the

cotyledons remaining undisturbed within the uterus. The allantoic and amniotic membranes are sealed over and *by suitable arrangements with plastic bags it is possible to collect the urinary and oropharyngeal contributions separately* [italics added]. At the same time, the amniotic and allantoic fluids (without fetal contribution) are available for sampling. Pregnancy continues normally in these circumstances.

Bilateral fetal adrenal ablation and hypophyseal ablation have been consistently achieved in sheep without interruption of the pregnancy. The adrenals are surgically exposed and then injected with a sclerosing fluid. The hypophysis is similarly ablated by blind introduction of a specially designed cannula.

It is intended that these techniques should be exploited in the following ways:

The geographical separation of the components of the liquor amnii provides an ideal basis for the study of feto-maternal and materno-fetal transfer of water, electrolytes and other solutes, employing isotope labelled materials.

The bag enclosing the fetal head has been found to contain a high concentration of surface-active material [italics added]. Collaboration with other workers in the field of lung surfactants is proposed...

The effect of fetal adrenal and hypophyseal ablation on parturition will be studied. The opportunity to extend work on the part which the fetal adrenal plays in estrogen metabolism will also be available.

The scope of this plan of work may seem too wide. However, it should be emphasized that it represents a period of intensive work on techniques which have been carefully prepared during the past 3 years so that delays from unexpected technical difficulties should be minimal.

None of the above techniques has been reported previously. It is known that unsuccessful attempts at fetal adrenalectomy and hypophysectomy (by decapitation) in larger animals have been made at centers in the United States. There is suggestive evidence from the known association of postmaturity with human anencephaly [congenital absence of the brain] and from the work of Holm (1961) in fetal calves with adrenal and hypophyseal hypoplasia that the onset of labor is closely related to fetal adrenal function, but direct experimental support for this hypothesis is lacking.

The field of fetal physiology has been a somewhat neglected one when compared with the work done on the neighbouring periods of life—embryonic and neonatal. This has been largely due to lack of suitable techniques by which to come to grips with the fetus in its protected environment. Until recently, experiments have been usually of an acute nature and often under most unphysiological conditions. Techniques such as those described above allow a direct approach while at the same time preserving a physiological state as far as possible.

Although none of those who studied the flow of lung fluids went so far as to propose a prenatal diagnostic test (possibly because there was none then known that would detect lung surfactant diluted by a large pool of amniotic fluid), they cleared the way to analyze human amniotic fluid and see if pulmonary surfactant was present. The first clinical prenatal test to identify immature lungs was devised by Gluck and his associates. Over a five-year period (1967 to 1972), they had done a careful analysis of the biochemical development of the mammalian fetal lung and published a series of papers in *Pediatric Research*. They noted that immature lungs were strikingly deficient in a major component of surfactant (lecithin) and that amniotic fluid analysis could be used not only to chart normal maturation of the lungs *in utero* but also to identify those fetuses who were almost certain to suffer from respiratory distress syndrome at birth. They used the ratio of lecithin (L) to sphingomyelin (S) in amniotic fluid. In babies with maturing lungs, the L concentration rises sharply at 35 weeks of gestation, usually to two times that of S, and continues to increase while S levels off or decreases. Gluck extracted phospholipids from about 5 mL of amniotic fluid and measured the L/S ratio by thin-layer chromatography; the analytic procedure required about 1-1/2 to 2 hours (85). From this ratio he could now tell, before birth of the baby, whether the baby would (low ratio) or would not (high ratio) have respiratory distress syndrome. Knowing this greatly increased the baby's chances of survival if its mother was transported (by helicopter if need be) to a regional center staffed and equipped for, and dedicated to, intensive care of the newly born with respiratory distress syndrome (RDS), and the baby was born there.

It wasn't long before the need became apparent for a test that was as reliable as Gluck's, but faster, simpler, cheaper, and suitable for use in an office or even by a bedside. Clements and his group came up with one within the next year (86); it was based on Pattle's observation that where there was surfactant, there was stable foam. However, because other substances in amniotic fluid (proteins, bile salts, and salts of free fatty acids) can also form stable foam, Clements had to exclude these from the surface films; this he accomplished by adding a competitive (but nonfoaming) surfactant, ethyl alcohol. When he put equal volumes of 95 per cent alcohol and amniotic fluid in a tube and shook it, he found that when saturated lecithin (the kind that predominates in pulmonary surfactant) was present, foam formed and persisted for as long as several hours. Once one has obtained amniotic fluid, nothing could be simpler. The test does not require a highly trained biochemical technician; it needs only clean test tubes, pipettes, and 95 per cent alcohol. When amniotic fluid is not available, the test can be performed on fluid aspirated from the newborn's stomach, since this largely represents amniotic fluid, and maybe some tracheal fluid as well, that has been swallowed by the fetus.

Prevention of Respiratory Distress Syndrome

I said that basic data on the maturation of the lung might be clinically useful if (1) someone could develop a prenatal

test that identified immature lungs (and two someones did), and (2) something could be done to make these lungs mature before or very shortly after delivery of the baby. Two "somethings" come to mind: (1) delay delivery, if possible and safe, for a day or two, and (2) hasten, by pharmacological means, maturation of the fetal lungs without harming other organs. The latter would be impossible if cells that normally form surfactant or systems that should release it from these cells are congenitally absent or defective. But it would be possible if all the parts of the machinery are there and ready to function but haven't yet got the signal from the programming system to get going.

We now come back to Graham Liggins, the obstetrician-researcher from New Zealand, who had started with the clinical observation that babies who were born without a brain (anencephalic) and therefore without a complete pituitary gland were often born postmature. Recall that in his 1964 application, he wanted to do a lot of things with his special sheep preparation (he allowed that "the scope of this plan of work may seem too wide") and one of these was to determine the effects on delivery of removal or destruction of the fetal pituitary gland and of the fetal adrenals (whose secretions depend on a functioning pituitary)—in short, did *fetal* hormones influence the time of delivery? When he got back to New Zealand in 1966, he continued to study the effect of ACTH and adrenal corticoids on the time of delivery; if removal of the fetal adrenals leads to postmature delivery, would injection of cortical hormones into the fetus lead to premature delivery? He injected dexamethasone into 10 lambs and in early 1969 reported these remarkable observations (88):

> Gross examination of the lungs of ten lambs delivered spontaneously at 117-123 days after dexamethasone infusions showed that in six, none of which had been artificially ventilated, there was partial aeration. In most instances the aeration consisted of patchy expansion in the upper lobes, but in one lamb delivered at 123 days the lower lobes were also partly expanded. This lamb was found alive at least an hour after being born and survived for a further hour until killed. The body weight of 2,349 g., the general appearance and the bone age determined by X-ray of the limbs corresponded with the duration of pregnancy calculated from the date of mating. During the period of observation the lamb bleated and showed some signs of respiratory distress. Histological examination of the lungs removed 4 hours after death confirmed that alveolar expansion had been maintained....
>
> Cortisol is known to be capable of inducing precocious activity of a variety of enzymes in immature animals....
>
> The observations on the foetal lungs of lambs at 117-123 days gestational age may represent another example of precocious induction of enzyme activity by corticosteroids. According to Howatt, Avery, Humphreys, Normand, Reid & Strang (1965), and Reynolds, Jacobson, Motoyama, Kikkawa, Craig, Orzalesi & Cook (1965), maintenance of alveolar expansion in the lamb is dependent on adequate surfactant activity. These authors and also Brumley, Chernick, Hodson, Normand, Fenner & Avery (1967), found that alveoli collapse and the lungs become airless at maturities of less than 125-127 days. Persistence of partial expansion of the lungs in the corticosteroid-treated lambs in the present series at 117-123 days strongly suggests accelerated appearance of surfactant, possibly as a result of premature activity of enzymes involved in a biosynthetic pathway. [Later studies (89) showed that fetal lambs have no or very little surfactant in their tracheal fluid at 124-133 days of age.]

Liggins now had a long list of studies that had to be done but decided to pass his observations on lung maturation on to others who had laboratories better equipped than his to do the necessary biochemical, biophysical, and electron microscopic studies. One of these was Avery, who visited New Zealand in March of 1968. On her return home she and her associates, first at Johns Hopkins and then at McGill (DeLemos, Kotas, Wang, Thurlbeck, and others), mounted a thorough attack on the problems (90-94), which confirmed and extended Liggins's observations and provided a morphological and biochemical framework for them.

Liggins decided instead to see if adrenal cortical hormones behaved in the human fetus as they did in the lamb—would they hasten the maturation of babies whose mothers were in spontaneous, premature labor? In 1972, he reported (95):

> A controlled trial of betamethasone therapy was carried out in 282 mothers in whom premature delivery threatened or was planned before 37 weeks' gestation, in the hope of reducing the incidence of neonatal respiratory distress syndrome by accelerating functional maturation of the fetal lung.
>
> Two hundred and thirteen mothers were in spontaneous premature labor. When necessary, ethanol or salbutamol infusions were used to delay delivery while steroid or placebo therapy was given. Delay for at least 24 hours was achieved in 77% of the mothers. In these unplanned deliveries, early neonatal mortality was 3.2% in the treated group and 15.0% in the controls (p 0.01). There were no deaths with hyaline membrane disease or intraventricular cerebral hemorrhage in infants of mothers who had received betamethasone for at least 24 hours before delivery. The respiratory distress syndrome occurred less often in treated babies (9.0%) than in controls (25.8%, p 0.003), but the difference was confined to babies of under 32 weeks' gestation who had been treated for at least 24 hours before delivery (11.8% of the treated babies compared with 69.6% of the control babies, p 0.02).
>
> There may be an increased risk of fetal death in pregnancies complicated by severe hypertension-edema-

proteinuria syndromes and treated with betamethasone, but no other hazard of steroid therapy was noted.

We conclude that this preliminary evidence justifies further trials, but that further work is needed before any new routine procedure is established.

Has further work established a role for pharmacological acceleration of lung maturation to prevent RDS? Apparently not if administered to a baby already born (because, postnatally, most infants with RDS have a marked increase in cortisol concentrations in plasma by 6 to 12 hours of age, presumably owing to the stress of the disease), but there *is* a role for adrenal cortical hormones given to mothers before delivery. There is agreement that the benefits clearly outweigh possible risks and that treatment with corticosteroids is indicated when prenatal tests of amniotic fluid are positive for RDS (negative for surfactant) and when delivery can be delayed safely for 24 hours (96).

Again, it is only fair to mention that someone else was the first. In 1950 (97), Provenzano treated a newborn baby with hypofunction of its adrenal cortex, using Upjohn's adrenocortical extract. Because Provenzano didn't begin this treatment until the 13th postnatal day, it is unlikely that the baby had RDS or immature lungs, but the baby's respiration improved, and its lungs (formerly collapsed) expanded. This encouraged Provenzano to use adrenal cortical extract in a controlled study with 118 untreated newborn babies and 118 treated with adrenal cortical extract (98); 16 untreated babies had prolonged and difficult grunting and retracting respirations and only 8 treated babies had these symptoms. He concluded by hoping "that other investigators will evaluate the use of this substance for newborn infants showing ill effects from anoxia ... in order that the true value of adrenal cortex extract be established." I don't believe others did; Provenzano is not mentioned by Liggins, Avery, and others currently working on lung maturation by adrenal cortical hormones. If others had repeated his *postnatal* use of adrenal cortical extracts, they probably would have had disappointing results, for reasons just mentioned; it seems that the therapeutic value of corticoids had to be established by experimental obstetricians who studied the immature fetus *in utero*.

Buckingham and associates in an 18-line abstract published in 1968 (99) called attention to the work of Moog, who showed that maturation of fetal epithelial cells in the small intestine was enhanced by corticosteroids, and they wondered whether lung cells (which are derived embryologically from the same tissue as gut) might behave similarly. Buckingham died soon thereafter and there is no complete report. Liggins, who had already been working for several years with adrenal cortical hormones and fetal maturity, knew that cortisol could induce precocious activation of enzymes in immature animals and in his 1969 paper cited five references to this observation between 1955 and 1966. If he had not, Buckingham's few lines might have been the ones that triggered research in lung maturation.

Treatment of Respiratory Distress Syndrome

If all neonatal respiratory distress were due only to immaturity of fetal lungs at the moment of delivery, *if* neonatal diagnostic tests invariably spotted this, and *if* preventive measures (delaying delivery and speeding up lung maturation) always worked, there would be no need for *therapy*. But there are too many *ifs* involved and it is likely that intensive care will remain the backbone of treatment for another decade or two.

Intensive care involves many things: besides providing adequate pulmonary ventilation, it also means maintenance of nutrition, fluid balance, blood volume, and blood pressure, prevention or management of infections, maintenance of body temperature, and correction of congenital defects. Crucial to survival, of course, is providing adequate pulmonary ventilation. But even though all types of assisted, controlled, or mechanical ventilation useful in adults were tried in newly born babies with RDS, the mortality rate remained high. It is hard to compare mortality rates in different nurseries because each team has somewhat different criteria for the severity of RDS and for beginning a particular form of therapy, and of course each baby has its own complicating factors. And mortality rates are always higher in babies born early in gestation and lower in those born at or close to term, and physicians who compare the value of one procedure with another must always take gestational age into account. (It is usually estimated, though far from precisely, by the weight of the newly born baby.) Thus, in 1969, data collected by Swyer (100) from 6 hospitals on 289 babies with RDS who required artificial ventilation showed that of 2 babies who weighed less than 1,000 grams at birth, neither lived; of 64 babies who weighed between 1,001 and 1,500 grams, only 12.5 per cent lived; of 82 who weighed between 1,501 and 2,000 grams, 29 per cent lived, and of 141 who weighed more than 2,000 grams, 57 per cent lived.

In that same year, Gregory, Kitterman, Phibbs, Tooley, and Hamilton began to use continuous positive airway pressure (abbreviated CPAP and sometimes pronounced C-PAP), instead of intermittent positive pressure, in managing ventilation in babies with RDS; the method supplied a pressure of 6 to 12 mm Hg *throughout* the respiratory cycle while the infants breathed spontaneously, usually through an endotracheal tube. Their results, published as an abstract in 1970 (101) and as a full report in 1971 (102), were dramatic. Of 36 babies with RDS, all of whom had a P_{O_2} of arterial blood of 50 mm Hg or less despite the use of O_2 and positive pressure ventilation with a bag and mask, 32 (89 per cent) lived. Of their 12 RDS babies weighing between 1,000 and 1,500 grams, 83 per cent lived; of 11 babies weighing between 1,501 and 2,000 grams, 91 per cent lived; of 12 who weighed more than 2,000 grams, all lived. One who weighed 930 grams died. Nothing had changed in their intensive neonatal care unit between 1965-1966, when only 11 per cent of their 1,000-1,500 gram babies had survived, and 1969-1971 when 83 per

cent lived,† except for the use of CPAP. Soon nursery after nursery repeated and practically all confirmed the amazing results. *Medical World News* quoted Mary Ellen Avery in a January 1972 interview (103):

> Dr. Avery, who was one of the *NEJM* referees for Dr. Gregory's first report, has seen the results of CPAP at Montreal Children's Hospital.
>
> "You can't challenge this one when you see these babies," she says. "Everything Dr. Gregory says is absolutely true. Everyone around the country who has tried to use it comes up with eyes bugging and says, 'My goodness, it works!' What's so dramatic about it is that it happens within minutes. You can see it! I have no problem giving it unqualified endorsement. CPAP saves babies."

Now the main reason for using a retrospectroscope is to try to determine *why* certain advances in science occurred when they did—whether rapidly or slowly. Before 1959, there was no solid experimental basis for using CPAP in treating babies with RDS, but in 1959 there was. If you read or reread page 521 of Avery and Mead's 1959 report (104), you will find the statement:

> Thereafter [after the first inspiration], during expiration, the alveolar surface of the *normal* lung would have diminished tension, thus reducing the tendency of the air spaces to collapse. On the other hand, in a lung lacking this lining material, surface tension would tend to remain high during expiration; the air spaces would be unstable, and some would collapse.

And if you read page 720 of Brown, Johnson, and Clements's (105) report in the same year, under *Discussion* you will find:

> The uniformity of the results obtained in these several methods and preparations argues strongly for the presence of a peculiar material on the alveolar surface. Its minimum coefficient of compressibility is between 0.01 and 0.02 cm/d. This value places it in the category of 'liquid' films. The film can apparently be reversibly compressed to 50% of its initial area. After further compression, the film apparently ruptures on re-expansion. This suggests a solidification or gelation, or folding on marked compression which is irreversible.

These two paragraphs almost spell out the proper physical and physiological approach to ventilating the lungs of babies with RDS: Keep the alveoli open or they'll collapse on each expiration. If they do, the surface film will rupture irreversibly and not reform on the next inspiration. Alveolar collapse therefore places a severe strain on both the baby's inspiratory muscles and on its limited ability to synthesize new surfactant (to replace that destroyed during alveolar collapse).

With these observations pointing to the use of greater than atmospheric air pressure during expiration to counter the likelihood that the combined forces of elastic tissue recoil and surface tension would collapse alveoli, why were there no published reports of its successful use until 1970-71?**

One reason, in my opinion, was the old and continuing problem of the *name* of this disorder. Almost everyone called it hyaline membrane disease or respiratory distress syndrome (though one group called it the pulmonary hypoperfusion or pulmonary ischemia syndrome); few called it by its old name, atelectasis of the newborn. Perhaps if there had been no compulsion to change the name, more emphasis would have been placed on treatment designed to counteract alveolar collapse during expiration.

Another was that there were no modern intensive care units for the newly born until Mildred Stahlman's in 1963-64 and until then no one had systematically developed apparatus and tests for monitoring and measuring the physiological and biochemical state of these tiny and fragile creatures. Others soon followed Stahlman and permitted the scientific study and care of the newborn to spread.

A third reason was that some were intent on the wholly worthy effort of correcting the cause of the disease rather than treating it nonspecifically. When the chemical nature of surfactant became known (though in retrospect not fully) and pure dipalmitoyl lecithin became available, it seemed logical to try to replace natural surfactant by aerosols of DPL (107, 108). And when pulmonary ischemia was found to cause atelectasis associated with a deficiency of surfactant (109), it seemed desirable to improve pulmonary arterial blood flow.

But a fourth and probably more important reason was that World War II research pointed out several risks involved in the use of pressure breathing. Pressure breathing was tried between 1942 and 1945 as a means of permitting pilots of fighter planes to get to higher altitudes. After the war, it came into clinical use as controlled positive pressure ventilation of patients in operating rooms and as part of the management of several cardiopulmonary disorders in adults. Physiologists and anesthesiologists tested a variety of devices that produced a wide range of ventilatory patterns: short inspiration-long

†In 1975-76, 93 per cent in this weight group lived.

**I don't know how many pediatricians, obstetricians, or anesthesiologists tried CPAP (or some modification) without success and without reporting on their attempts. I know that Avery tried in at least one baby, Hamilton in two, Tooley in one, but none had enough success to continue at that time. And in 1972, Auld, Krauss, and Klain wrote a letter to the Editor of *Pediatrics* (106), telling of their unpublished 1968 attempt to treat four babies with RDS with continuous distending pressure with success for a few hours, followed by failure in three of the four.

expiration, long inspiration-short expiration, rapidly versus slowly rising pressures during inspiration, rapidly versus slowly falling pressures during expiration, and positive pressure during inspiration coupled with negative (subatmospheric) pressure during expiration.

These studies showed that whatever increase in intra-alveolar pressure was transmitted through the lungs to the pleural cavity raised intrathoracic pressure, opposed the flow of blood into the intrathoracic venae cavae, and decreased venous return to the heart. This might be useful in treating patients with pulmonary vascular congestion but not in patients with low systemic arterial blood pressure. Figure 4, from a study by Cournand, Motley, Werkö, and Richards in 1948 (110), shows the effect of 3 different patterns of ventilation on mean pressure throughout the respiratory cycle; Werkö in his review article (111) summarized the situation succinctly by writing, "If no influence of pressure breathing on the circulation is desired, the mask pressure during the expiration should be kept as near atmospheric as possible." Beecher and associates were even stronger in their statement (112): "In animals [dogs] with poor circulation, increased pressure in the airway was deleterious and could cause death." Because premature babies with RDS are apt to have a low blood volume and suffer from circulatory shock, pediatricians were wary of positive pressure breathing and particularly of any variety of it that increased *mean* intra-alveolar pressure throughout the respiratory cycle, which of course is exactly what CPAP does.

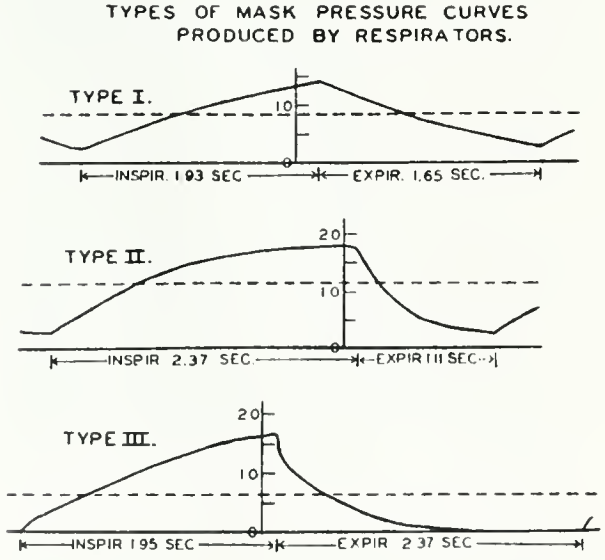

Fig. 4. Three types of mask pressure curves observed during studies of *intermittent* positive pressure breathing. The dotted line is the *mean* mask pressure for the entire respiratory cycle. Note that rapidly rising and prolonged inspiration (type II) produces the highest mean pressure. (From Cournand and associates [110]; reprinted by permission of publisher.)

But, in retrospect, these studies on adults or dogs didn't really apply to the lungs of babies with RDS in which pulmonary compliance was greatly increased and pretty uniformly so. Otis, Rahn, and Fenn (113) had pointed out in 1946 that the fraction of intra-alveolar pressure transmitted to the intrathoracic cavity was not a fixed and therefore predictable one but depended on the distensibility of the lungs. Further, Price and associates (114) made the clinical observation in 1951 that positive intrapulmonary pressure, as high as 22 to 25 cm H_2O, failed to decrease arterial blood pressure in patients profoundly anesthetized with cyclopropane, in part because the increased intra-alveolar pressure raised venous pressure only 9 to 11 cm H_2O in their patients as compared to 11 to 15 cm H_2O in conscious subjects.

Gregory and colleagues tested this point in their newborn babies with RDS and found that only 20 per cent of the air pressure applied to the airways was actually transmitted to the intrathoracic, extrapulmonary structures. Later, Herman and Reynolds (115) found almost no transmission of increased airway pressure to a balloon placed in the baby's esophagus and concluded that there is little risk of producing adverse circulatory effects by using high airway pressures during acute stages of severe RDS in babies; like Gregory and associates, they warned that airway pressures should be decreased when pulmonary compliance begins to return to normal values. Again, it is worth noting that the development of intensive care units for babies made possible such monitoring and measurements.

Who was Gregory and how did he become involved in this story? In 1961-62, William Hamilton, then Chairman of the Anesthesia Department at the University of Iowa, spent a sabbatical year at the University of California in San Francisco working with Clements and Tooley on atelectasis that occurs during temporary experimental occlusion of a right or left pulmonary artery in dogs, presumably because during the period of pulmonary ischemia, there is no substrate brought to alveolar cells that form pulmonary surfactant (116). As an anesthesiologist, he had been interested in ventilation of the lungs of patients with an open thorax and also in the causes and management of postoperative atelectasis and had occasionally used continuous positive airway pressure to relieve certain types of airway obstruction. From Clements and Tooley, he learned about pulmonary surfactant and a new type of atelectasis or alveolar collapse, and about problems arising from mismatched flow of air and blood to alveoli.

On his return to Iowa, he decided that when the opportunity arose, he would use his "tight bag" technic to distend alveoli of babies with RDS. In 1963-64, several newborn babies were dying, despite the use of a respirator, and Hamilton worked throughout the night, maintaining a positive pressure in their airways. Babies about to die made a remarkable temporary recovery but became worse the next day; however, the *immediate* improvement made a lasting impression on Hamilton.

That same year Tooley, Clements, Klaus, and several colleagues decided to spend 6 months working in the delivery

rooms and nurseries of the Kandang Kerbau Hospital in Singapore (where 40,000 babies were delivered each year, and more than 300 of these had RDS) to see whether they could replace the missing natural surfactant on the alveolar surfaces by aerosolized dipalmitoyl lecithin. Hamilton wanted to join the research team in Singapore to test the usefulness of his "tight bag" technic to distend lungs throughout the respiratory cycle, but the group concluded that it would be difficult enough to test one hypothesis (replacement therapy) in a 6-month period without trying to test two. The decision was of course correct in principle, although, in retrospect, it can be questioned (117).

Why this long parenthetical piece about Hamilton when I started to answer the question, "Who was Gregory?" Gregory had been a medical student at the University of California in San Francisco (M.D., 1963). He became interested then in RDS as a result of a lecture in obstetrics. After an internship at UCLA, he served 3 years as a resident at UCSF, one in surgery and two in anesthesia (1965 to 1967). During his anesthesia residency, he spent a lot of time in the delivery room and nursery with Tooley, Kitterman, and Phibbs, helping them in their attempts to improve the treatment of asphyxia. This was in the early days of intensive care units; Day in Kansas had organized the first coronary care unit in 1962-63 and Mildred Stahlman at Vanderbilt had developed the first genuine neonatal intensive care unit about 1963 or 1964. Tooley started his about 1965-66. Anesthesiologists were ideally trained to play an important role in these and were becoming interested and involved; Gregory was one of these.

Now at last we can connect Hamilton and Gregory. Stuart Cullen, Chief of Anesthesia at UCSF, couldn't resist the "call" to be Dean in 1966, and in 1967, Hamilton, still deeply interested in RDS, came to San Francisco to take Cullen's old job as Chairman of Anesthesiology. Gregory was committed to a year's research fellowship in 1967-68, but at the end of that year, Hamilton assigned Gregory to a full-time position in the intensive care unit for the newborn with no responsibilities for giving anesthesia. For those not familiar with the economics of hospital care, I must add that it requires real conviction on the part of a professor of Anesthesia to assign one of his staff to work full time in the nursery instead of to regular duty in surgical operating and recovery rooms, but Hamilton was, at least vicariously, back in the RDS business.

One night there was no one in the nursery but Gregory, nurses, technicians, and a baby with RDS in its last minutes of life despite the use of O_2-intermittent positive pressure breathing. This was not the time to worry about transmission of pressure from airways to the intrathoracic space. (And there was really no need to because Phibbs and Kitterman at UCSF had long concentrated their efforts on correcting hypovolemia, low blood pressure, and decreased cardiac output in the newly born from the very moment of birth.) Gregory decided to use CPAP and the baby lived. An added dividend was that, because CPAP opened alveoli perfused with mixed venous blood and therefore oxygenated this blood, its use permitted treating the baby with lower (and safe) concentrations of inspired O_2 and thereby lessening or eliminating the toxic effects of O_2 on the lungs. (Frequent analyses of O_2 tension of arterial blood eliminated the other bugaboo of O_2 inhalation in the newly born—blindness due to retrolental fibroplasia.)

By 1970, the results of treating seven babies (six of whom survived), were reported to the Society for Pediatric Research, and in June 1971 the results of treating 36 babies (see page 716) were published in full. Why didn't it come in 1959-61 instead of 1969-71? I've mentioned some of the important reasons: need for the neonatal intensive care unit, need to test other forms of treatment, fear of adverse effects of CPAP on the circulation.

Why Gregory rather than A, B, or C? One reason was Hamilton's continuing faith in CPAP despite earlier setbacks. Another, of course, was Gregory's close relation with a large group of RDS investigators. Gregory gives several other reasons that influenced him.

One was that Harrison and his associates (118) had shown that babies who grunted (breathed out against an expiratory resistance, self-imposed) improved, but when Harrison introduced an endotracheal tube into these same babies, and they could no longer grunt, they got worse. A somewhat similar situation had been encountered by Smith and associates (119), who noted improvement in oxygenation of arterial blood of babies with RDS when a mechanical ventilator kept the intra-alveolar pressure above atmospheric for more than half of the baby's respiratory cycle.

Another was that newborn babies usually breathe rapidly—60/min or more. When a newborn baby was ventilated with a positive pressure device cycling at a rapid rate and there was not enough time during expiration for the alveolar and airway pressure to fall to atmospheric, the baby got better; when the machine malfunctioned at the high frequency and had to be used at a low frequency, the baby got worse. Gregory decided that when babies with RDS *did* breathe voluntarily, he would let them continue to do so (with a continuously imposed distending pressure) and not permit use of a slower rate of mechanical ventilation.

I suspect that in any case, CPAP was a treatment whose time had come. RDS was the most important life-or-death problem in pediatrics, more and more highly trained pediatricians were working in intensive care units for the newborn, and it was inevitable that someone in the proper environment would try CPAP, with the proper pressures. Llewellyn and Swyer came close in 1970 when they, like Gregory, reported their results to the Society for Pediatric Research (120); they added positive expiratory pressure (2.5 to 6 cm H_2O) to mechanical ventilation of 11 infants with RDS (mean birth weight 2,160 grams) and 7 (64 per cent) survived. Gregory used 8 to 16 cm H_2O pressure (6 to 12 mm Hg) continuously in babies breathing spontaneously without a ventilator.

Trials and Tribulations

Physicians engaged in clinical trials on the human fetus and newborn have special tribulations in addition to the usual ones. The special tribulations are that they are damned by some if they *don't* do research and damned by others if they *do*. The usual criticisms relate to the design of a therapeutic study and might be summed up by two questions: (1) Is the double blind, randomized clinical trial the only scientifically acceptable design? (2) Is this type of trial often scientifically unnecessary and ethically unacceptable?

Because there is currently a lively debate on these questions (121-125) and because the study of Gregory and his associates was not double blind and randomized, I should comment a bit on introducing new forms of treatment. I've done clinical investigation of therapeutic procedures as well as purely laboratory studies. One of my clinical studies with Dripps (the effect on healthy men of inhalation of O_2 for 24 hours versus inhalation of air for the same time) was as well controlled as a randomization enthusiast could want. But another was not. It was a nonrandomized comparison of the efficacy of two methods of artificial ventilation. It couldn't possibly have been randomized because there wasn't any control group—each patient served as his own control. In 1946, when Dripps and I found that, in adult apneic patients, the Eve (tilting) method moved 500 mL air/breath and, in the same patient, the Schafer method moved only 75-117 mL (not enough even to clear the respiratory dead space), we realized that each-patient-as-his-own-control was the best way to determine which method was better. In our opinion, we would have served science poorly and morality even worse if we had randomly assigned each apneic patient to one of two groups and treated one with a method sure to fail (and now abandoned as worthless) and the other with a pretty good technic.

Statistician A. Bradford Hill (126) in 1951 pleaded for and obtained the controlled clinical trial; worshippers at his altar would do well to reread his original paper in which he stated:

> The first step in such a trial is to decide precisely what it is hoped to prove, and secondly whether these aims can be ethically fulfilled. It need hardly be said that the latter consideration is paramount and must never, on any scientific grounds whatever, be lost sight of. If a treatment cannot ethically be withheld then clearly no controlled trial can be instituted.
>
> ...Sometimes, not often, controls are indeed unnecessary. If in the past a disease has invariably and rapidly led to death there can be no possible need for controls to prove a change in the fatality rate. Thus the trial of streptomycin in tuberculous meningitis needed no control group. Given a precise and certain identification of the case, the success of treatment could be measured against the past 100% fatal conclusion. No controls, too, are essential to prove the value of a drug such as penicillin which quickly reveals dramatic effects in the treatment of a disease. Such dramatic effects occurring on a large scale and in many hands cannot be long overlooked.

It seems to me that there is a fairly sensible way of looking at clinical investigation that involves the medical or surgical management of patients: assuming that you agree with Bradford Hill that ethical considerations (the patient's right to life and happiness) supersede scientific ones, then do the very best study that *needs* to be done. Sometimes it will require no concurrent controls (e.g., when a drug or procedure leads to the almost invariable and complete cure of a disease previously almost invariably fatal); sometimes the best study requires treating all patients similarly, first with procedure A and then with procedure B, or vice versa (the sequential approach, or each-patient-as-his-own-control); sometimes the best study does indeed require a randomized, double blind, large scale and very expensive study to settle a question, such as whether gobbling huge doses of ascorbic acid daily prevents the common cold, and here the rigidly controlled trial ought to begin at least as early as the second patient is treated. But let's not live in constant fear of the great god Randomization; his (or her) appetite is huge, and, if fed continuously, could consume much of the nation's research dollars and personnel, and even the lives of some patients.

Clinical trials in the nursery differ somewhat from trials in children or adults. The blood pressure of an adult with hypertension is affected psychologically by his confidence in his physician; the life of a premature baby in the nursery is not. In the nursery, the color or taste of a placebo has no influence on the baby's will to live. In the nursery, the physician and nurse cannot be "blinded" to the therapy used, because they themselves must administer it; and they must know vital measurements minute by minute to carry out optimal therapy. In the nursery, immediate survival and preservation of organ function is all that counts.

Now let's look at the classic study of Gregory and his colleagues between 1969 and 1971. It *did* include two important controls: (1) It had the experience, over a period of years, of a highly expert group, schooled and skilled both in modern research technics and in intensive and continuous monitoring and care of the newborn so that it had unusually good records of the clinical, physiological, and biochemical state of both pre-CPAP treated and post-CPAP treated babies—in short, the group was unusually well equipped to identify and compare the results in RDS babies treated in 1966, 1967, 1968, 1969, etc. (see p. 716 and footnote p. 717). (2) At least initially, the group used each baby as its own control, first using modern intensive care and intermittent pulmonary ventilation and then the same modern intensive care with only one change, a switch to *continuous* positive airway pressure.

Let's ask how one would have obtained permission to do a randomized, controlled clinical study in the nursery in 1969 to 1971.

SCENARIO

Enter physician.
Physician to mother: Your baby has respiratory distress syndrome. We want to compare a new method of treatment, A, with the present management, B. Can we enter your baby in this study? It would be assigned randomly to treatment A or B.
Mother: In your opinion, does my baby have a better chance of living with treatment A or B?
Physician: We don't know. Maybe A, maybe B.
A space-age computer interrupts at this point: Not true. Physician incorrect. Answer unacceptable. He knows A is better because 5 babies in a row have lived with treatment A which is at least twice as good a record as treatment with B.
Physician (now speaking honestly): We're convinced that A is far better but we can't convince Drs. X, Y, and Z unless we have a randomized, controlled clinical study.
Mother: Thanks; I want a live baby more than anything else in the world—even more than convincing Drs. X, Y, and Z. *Please* be sure my baby gets the new treatment.
Exit Mother.

Follow-up: The twins in figure 5 are happy that one of them was not assigned to a control group that was not treated with CPAP.)

Fig. 5. Twin girls born in 1974 after 29 weeks' gestation. Birth weights were 1,100 and 1,160 grams. Both had assisted ventilation from birth. *(Upper left)* Twin A at 1 day of age, breathing against continuous positive pressure of 9 mm Hg. The tip of an umbilical artery catheter lies just above the bifurcation of the aorta; the catheter is used to obtain continuous measurements of arterial blood pressure and periodic samples of blood to measure its O_2 tension. (The size of each infant can be estimated from the diameter of the transparent corrugated tube [top right], which is 2.8 cm.) Twin A required ligation of a patent ductus arteriosus in her fourth day of life to relieve congestive heart failure. She received CPAP or positive end-expiratory pressure until the age of 24 days, when the endotracheal tube was removed. At 2 and 3 years of age, she performed within the normal range on standard infant intelligence tests. *(Upper right)* Twin B at 1 day of age breathing against a positive airway pressure of 10 mm Hg. She too required surgical ligation of a patent ductus arteriosus at 4 days of age. She was treated with CPAP or positive end-expiratory pressure until 21 days of age, when the endotracheal tube was removed. Intellectual performance at age 2 and 3 years was similar to that of Twin A. *(Lower)* Twins A and B at age of 2 years. *(Photographs courtesy of Dr. William Tooley.)*

Some believe that the time is now ripe for controlled studies, with randomization, designed to evaluate finer points of treatment, to achieve the lowest possible mortality and morbidity (127): what type of distending pressure is best? with what concentration of oxygen? when and for how long should it be applied?

Where Are They Now?

Neergaard, as mentioned earlier, died in 1947 before he had the satisfaction of seeing his work repeated, accepted, acclaimed, and canonized.

Gruenwald, after his 1946 research, made pressure-volume measurements of a very large series of lungs of infants who came to autopsy. In the early 1960s, while Associate Professor of Obstetrics, Pediatrics, and Pathology at Johns Hopkins, Gruenwald collaborated with Clements, then at Edgewood, Maryland, correlating the mechanical properties of infants' lungs with the surface activity of extracts made from them. He continued to publish papers on infant lungs throughout the 1960s. In 1968 he moved to Philadelphia, first to the Veterans Administration Hospital and the Department of Pathology at the University of Pennsylvania and, two years later, to Hahnemann. He has recently retired and is now Professor Emeritus of pathology at Hahnemann Medical College.

Macklin became Professor of Histology and Embryology at the University of Western Ontario in 1921 (a position he held for the remainder of his academic career). He was elected to the Royal Society of Canada in 1924 and to numerous other societies in North America and Europe. His own university awarded him the honorary degree of D.Sc. in 1953 when he retired at age 70. Because the policy of his university denied its facilities to retired faculty members, he continued his studies at home "with old sections and an old microscope." He died suddenly from a coronary occlusion on November 23, 1959, at age 75.

Radford, after his first published paper, which dealt with alveolar surface area, made a number of additional lasting contributions to our knowledge of artificial respiration and the mechanical properties of the lungs. He then became interested in the air we breathe, in toxic substances in it (such as carbon monoxide and its effects on the heart) and in toxic chemicals in cigarette smoke (such as polonium-210 and its possible role in producing lung cancer). From time to time he returned to his first research interest (renal physiology, water metabolism, and the antidiuretic hormone). He has had positions at DuPont's Haskell Research Laboratories, again at Harvard, then at the University of Cincinnati, and now seems to be well settled at Johns Hopkins, where he has been Professor of Environmental Medicine since 1968, except for a year at Oxford (1975-76) as Visiting Professor to the Department of the Regius Professor of Medicine. As one would expect, he has served in many important roles as consultant on environmental medicine to state and national bodies and has always maintained his interest in teaching and training others.

Pattle has remained at the Chemical Defence Research Establishment where he has been Senior Principal Scientific Officer since 1963. He has continued research on inhaled toxic materials and on his first love—the action potential of nerve and muscle—but, since 1972, has published exclusively on lung surfactant: the effect of anesthetics and some chemical agents on it, electron microscopic studies, and comparative anatomy and physiology of surfactant.

In a recent letter to me (June 11, 1977), he wrote:

> Now one or two cautions. First, the words "surface active." In ordinary physical chemistry this means "tending to accumulate at a surface and lower surface tension." Unfortunately in specialist lung literature, it has come to mean "capable of forming a surface film which, when compressed, can assume a metastable state of high surface pressure and reduce the surface tension to a small fraction of its equilibrium value." I have floated the word "surpellic" to describe substances of the latter type and films formed from them. It is highly undesirable that we should use "surface active" in a sense different from the ordinary. It even seems to confuse writers on the lung. I hope that "surpellic" (from Latin "pellere," to push) will catch on (see J. Zool., 182:125-136, 1977).
>
> Secondly, some writers refer to a discovery based on observation of something which was not what was actually being investigated, as a "chance" or "accidental" discovery. This is *never* true. Observations are made because the observer is on the lookout for anything strange. The discovery of lung surfactant came about as the result of a peculiar concatenation of circumstances, but not as the product of chance or accident.
>
> Von Neergaard deduced that the surfactant must exist, but he failed to find it for the following reason. He measured the surface tension by a method—i.e. measurement of the force necessary to pull a stirrup away from the surface—in which the surface was *stretched* at the moment of measurement. As the surfactant only shows its surpellic properties when the surface film is *compressed*, such a method could not detect it. In both the bubble and [Clements's] Wilhelmy trough methods the surface is *compressed*, so that the surfactant can be detected by these methods.

Clements left the Army Center for a year to be Visiting Professor in the Cardiovascular Research Institute, University of California, San Francisco, returned to Edgewood for a year, and then accepted a permanent faculty position in San Francisco where he still works as Professor of Pediatrics and Career Investigator of the American Heart Association. He was elected to the National Academy of Sciences in 1974 and has received many awards.

It may seem odd that Clements, who has always worked in the field of pulmonary and respiratory physiology, bio-

chemistry, and biophysics, receives his lifetime professorial salary from the American Heart Association (AHA) rather than from the American Lung Association. The AHA started its Career Investigator program in 1951 and, over a period of years, its Research Committee has initiated about 14 lifetime awards. In 1962, the American Lung Association (ALA) (then the NTRDA) had not yet instituted a similar program (though the American Cancer Society had); a well-known pulmonary scientist sent a formal proposal to the American Thoracic Society (medical section of the ALA) asking that it and its parent body provide lifetime career professorships for innovative, creative scientists judged likely to be leaders throughout their scientific careers; the proposal also formally nominated Clements for such a position. The Society's committees considered the proposal sympathetically but turned it down in 1963 "because of the rather limited amount of money available." The American Heart Association awarded him a Career Investigatorship in 1964 despite the fact that Clements was and still is essentially a pulmonary biophysicist-physiologist.

It is of interest that both organizations derive their funds from contributions by the public and receive a somewhat similar amount each year. In 1963 the ALA received $31,093,111 (but had "limited funds"). In 1964 the AHA received $30,121,526 but went on to support its twelfth Career Investigator. The AHA interprets its mandate from the public one way; the ALA interprets its in another. The AHA's Committee on Research believed firmly that an important role for voluntary health agencies is the recognition and support of individuals with unusual talent for research, to free them for long periods from onerous responsibilities that interfere with their work. The ALA did not. It would be interesting some years from now to evaluate the results of these two different policies on the improvement of health.

Avery, after her research fellowship in Boston in 1957-59 with Mead, returned to Johns Hopkins where she became Associate Professor of Pediatrics in 1964. She left in 1969 to become Chairman of the Department of Pediatrics at McGill University, but since 1974 has been Chairman of Harvard's Pediatrics Department and Physician-in-Chief to Children's Hospital Medical Center in Boston. She has been a complete neonatologist and has done research on a wide variety of problems of the newborn; from 1970 on, however, she has been involved deeply and continuously in problems of lung maturation and ways of accelerating it and preventing RDS. In her spare time, she has written two widely used books, *The Lung and Its Disorders in the Newborn Infant*, now in its third edition, and (with A. J. Schaffer), *Diseases of the Newborn*, and chapters in 15 books.

Mead has never wandered from Harvard. He received his B.S. and M.D. there and, except for two years of Army service (1947-49), has been on the faculty of the Harvard School of Public Health continuously since 1950, Professor since 1965. Mead's first nine publications resulted from his Army experience and dealt with the relationship between temperature and peripheral blood flow. Once ensconced in Harvard, he turned to research on the physical properties of the lungs and has stayed with this problem continuously. He has been responsible for part or all of the research training of many now well-known scientists, and by his enthusiasm and dedication to research and his generosity with ideas, has catalyzed the research of many of his fellows and colleagues.

Concluding Remarks

Ritchie Calder divided scientists into two groups: those who make it *possible* and those who make it *happen* (128). In a period of 20-some years, respiratory distress of the newborn has advanced from a state of almost complete ignorance to one of the most completely characterized of all disorders—and both groups share the credit for this remarkable advance. Laplace, Young, Neergaard, Radford, Pattle, Clements, Liggins, and many others made it *possible*, and Avery, Gregory, Gluck, and many others made it *happen*. It's worth emphasizing that Laplace and Young lived 100 years before there was such a disorder as atelectasis of the newborn; that Neergaard did his classic study only to find out if the millions of tiny bubbles in the lungs (the air sacs) contributed a new and unsuspected type of recoil in expiration; that Radford wanted to measure the alveolar surface area just for the sake of acquiring new knowledge; that when Pattle was asked whether, by using antifoams, he could get rid of pulmonary edema foam (that blocked the airways of goats poisoned by phosgene), he was a physicist "who knew very little about the pulmonary or cardiovascular systems" and probably never heard of RDS; and that Clements was a physiologist-biophysicist who wanted primarily to learn whether Radford or Pattle was right. None of those "who made it possible" was at that time looking for something to help in the early diagnosis, prevention, or treatment of RDS.

Scarpelli, who in 1968 wrote the first scholarly monograph (129) on pulmonary surfactant (with more than 320 references to articles published at that time), summed up the story of discovery and application in one paragraph:

> In any science there are the discoverers and innovators whose contributions reside in their ability to look forward with true perspective. For the lung surfactant system these scientists are Drs. K. von Neergaard, R. E. Pattle, J. A. Clements, E. P. Radford, Jr., E. S. Brown, M. E. Avery, and J. Mead. There are those who extend and refine the science and continue to innovate. Their names are in the bibliography of this text. Then there is the reporter and author. His task is his responsibility and he can only hope that he has been objective, reasonable, and stimulating.

There's another lesson worth learning from the story of RDS. You've learned the lesson when you realize what all of the entries in the following list have in common:

measurement of molecular size and configuration
experimental ablation of pituitary gland
oxygen and carbon dioxide electrodes
measurement of intraesophageal pressure
high resolution electron microscope
chromatography and lipid chemistry
origin of amniotic fluid
nerve gas and respiratory paralysis
soap films and bubbles
laws of gravitation and planetary motion
electrophoresis; radioimmunology
conduction of electricity through stretched wire
phosgene poisoning and pulmonary edema
high altitude physiology
alveolar ventilation-blood flow ratios
pulmonary surface area
dipalmitoyl phosphatidyl choline
intensive coronary care units

Correct. Knowledge of each of the above, initially completely unrelated to RDS, was essential or helpful in saving the lives of babies born with premature lungs. So when someone asks you what's the good of all this research that's not specifically directed to immediately solving the problem of cancer or emphysema or congestive heart failure, tell him (or her) that essential clues, concepts, and methods often (usually) come from unrelated fields. And then show him the picture of twins A and B and ask if it isn't really all worthwhile. And if he (or she) isn't interested in human life but only in dollars, tell him that the March 1977 report of the Task Force on Respiratory Diseases of the NIH Division of Lung Diseases (130) includes an estimate that a primary prevention program for RDS (starting in 1977 at our present advanced position) would reduce the number of premature births in the United States each year from 500,000 to 350,000, would decrease the number of infants born with RDS from 50,000-70,000 to 35,000-47,000 and the number of deaths from 5,000-10,000 to 3,500-7,000, and reduce the costs of treatment by 75 to 150 million dollars.

One final remark. In the early 1900s, Boys had put his popular lectures, "Soap Bubbles" into book form ("meant for juveniles and for juveniles only") "in the hope that it may excite in a few young people some small fraction of the interest and enthusiasm ... awakened in the author [by previous lectures of G. F. Rodwill]." In his introduction, Boys remarked, "I hope that none of you are yet tired of playing with bubbles, because, as I hope we shall see, there is more in a common bubble than those who have only played with them generally imagine." (131)

I wonder whether Neergaard was stimulated to do his experiments because of Boys's book. I also wonder how many more advances are still hidden inside an ordinary soap bubble.

Julius H. Comroe, Jr.

NOTE: My sincere apologies to my many scientific associates and colleagues whose names should have but didn't appear in these three articles; I tried but found it impossible to write a scholarly review and interesting story in one and the same article.

ACKNOWLEDGMENT

I thank Drs. Avery, Clements, Gregory, Hamilton, Kitterman, Liggins, Pattle, Radford, and Tooley for telling me their recollections of people and events, Dr. Tooley for providing the before and after photographs of RDS twins treated with CPAP, and Dr. Mary C. Williams for providing previously unpublished electron micrographs showing the life and death of surfactant.

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AARC

43rd International Respiratory Congress
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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page of

Form Approved OMB No 0910-0291 Expires: 4/30/96
See OMB statement on reverse

FDA Use Only (Resp Care)

Triage unit sequence #

A. Patient information

1 Patient identifier
In confidence

2. Age at time of event:
or
Date of birth:

3. Sex
☐ female
☐ male

4. Weight
____ lbs
or
____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
☐ death (mo/day/yr)
☐ life-threatening
☐ hospitalization – initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other

3 Date of event (mo/day/yr)

4 Date of this report (mo/day/yr)

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1 Name (give labeled strength & mfr/labeler, if known)
#1
#2

2 Dose, frequency & route used
#1
#2

3. Therapy dates (if unknown, give duration) (from/to (or best estimate))
#1
#2

4 Diagnosis for use (indication)
#1
#2

5 Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6 Lot # (if known)
#1
#2

7 Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9 NDC # (for product problems only)
– –

10 Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1 Brand name

2 Type of device

3 Manufacturer name & address

4 Operator of device
☐ health professional
☐ lay user/patient
☐ other

5 Expiration date (mo/day/yr)

6.
model #
catalog #
serial #
lot #
other #

7 If implanted, give date (mo/day/yr)

8 If explanted, give date (mo/day/yr)

9 Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on (mo/day/yr)

10 Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1 Name & address

phone #

2 Health professional?
☐ yes ☐ no

3 Occupation

4 Also reported to
☐ manufacturer
☐ user facility
☐ distributor

5 If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

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Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the eve

ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling
- therapeutic failures

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

- 1-800-FDA-0178 to FAX report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 to report by phone or for more information
- 1-800-822-7967 for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

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Calendar of Events

AARC & Affiliates

July 15—Live Video Conference

"Initial Treatment for the Pediatric Patient in Respiratory Distress," Part 5 of the AARC's 1997 "Professor's Rounds" airs from 12:30 to 2 PM Eastern Time.

CRCE: 1 credit hour.

Contact: The AARC at (972) 243-2272.

July 16—Live Telephone Question-and-Answer Session

View "Asthma Disease Management: Using the Revised NAEPP Guidelines in Practice," Part 4 of the AARC's 1997 "Professor's Rounds," and participate in a live telephone question-and-answer session from 12:30 to 1 PM Eastern Time.

CRCE: 1 credit hour.

Contact: To receive the videotape and register for the teleconference, call the AARC at (972) 243-2272.

August 6–8—New Mexico Society

31st Annual Conference, "At the Hop," at the Albuquerque Convention Center and Double Tree Hotel, Albuquerque, New Mexico. The annual golf tournament, awards banquet, and Sputum Bowl are scheduled.

Contact: Brooke Patterson, VA Hospital, (505) 265-1711, ext 4998.

August 20—Live Telephone Question-and-Answer Session

View "Initial Treatment for the Pediatric Patient in Respiratory Distress," Part 5 of the AARC's 1997 "Professor's Rounds" and participate in a live telephone question-and-answer session from 12:30 to 1 PM Eastern Time. CRCE: 1 credit hour.

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August 21—Ohio Society

Annual Critical Care Seminar, "Rock-n-Roll and Respiratory Care," hosted by MetroHealth Medical Center, Cleveland, Ohio.

Contact: Bob Messenger at (216) 778-3226 or e-mail bmessenger@mhmc.org.

August 26—Live Video Conference

"Nitric Oxide: Issues and Answers," Part 6 of the AARC's 1997 "Professor's Rounds" series, airs from 12:30 to 2 PM Eastern Time.

CRCE: 1 credit hour.

Contact: To register, call the AARC at (972) 243-2272.

September 8—Live Telephone Question-and-Answer Session

View "Nitric Oxide: Issues and Answers," Part 6 of the AARC's 1997 "Professor's Rounds" series and participate in a live telephone question-and-answer session from 12:30 to 1 PM Eastern Time.

CRCE: 1 credit hour.

Contact: To receive the videotape and register for the teleconference, call the AARC at (972) 243-2272.

September 17–19—Maryland and District of Columbia Societies

16th Annual Educational Symposium, the Conference by the Sea, "Respiratory Care Practitioners Reaching for the Future," at the Sheraton Fountainbleau Hotel, Ocean City, Maryland. A management track on managed care issues is also featured.

Contact: Elgloria Harrison at (410) 578-8600, ext 211.

Other Meetings

August 22–23—The American College of Chest Physicians

Pediatric Pulmonary Update at the ACCP Alfred Soffer Educational Center, Northbrook, Illinois.

Contact: ACCP, Product and Registration Services, 3300 Dundee Rd, Northbrook IL 60062, (800) 343-2227, fax (847) 498-5460, e-mail: registration@chestnet.org.

September 12–13—Atlanta Post-Polio Association

Post-Polio Conference, "Been There, Done That, Movin' On," at the Atlanta Marriott Gwinnett Place, Atlanta, Georgia.

Contact: APPA, PO Box 250566, Atlanta GA 30325; or Linda Sutherland at (770) 732-9163; or the APPA information line at (404) 350-7631; or e-mail bgbonham@mindspring.com.

September 19-21—Extracorporeal Life Support Organization
Ninth Annual Meeting at the Atheneum Suite Hotel, Detroit, Michigan.
Contact: Phoebe Hankins at (313) 998-6600 or e-mail at phankins@umich.edu.

September 25–26—INFOCARE
Second Annual Neonatal/Pediatric Respiratory/Critical Care Symposium at the Sheraton Fiesta Beach Resort, South Padre Island, Texas.
Contact: Ralph Miller, INFOCARE, 350 San Roman Rd, Los Fresnos TX 78566, (210) 233-5645 or fax (210) 233-1010.

American Association for Respiratory Care

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Primary Job Responsibility (check one only)

- ☐ Technical Director
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Type of Business

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- ☐ Other, specify _____

Date of Birth (optional) _____ Sex (optional) _____

U.S. Citizen? _____ Yes _____ No

Have you ever been a member of the AARC? _____

If so, when? From _____ to _____

Preferred mailing address: ☐ Home ☐ Business

For office use only

FOR ACTIVE MEMBER

An individual is eligible if he/she lives in the U.S. or its territories or was an Active Member prior to moving outside its borders or territories, and meets ONE of the following criteria: (1) is legally credentialed as a respiratory care professional if employed in a state that mandates such, OR (2) is a graduate of an accredited educational program in respiratory care, OR (3) holds a credential issued by the NBRC. An individual who is an AARC Active Member in good standing on December 8, 1994, will continue as such provided his/her membership remains in good standing

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE.

Place of Employment _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. (_____) _____

Medical Director/Medical Spansar _____

FOR ASSOCIATE OR SPECIAL MEMBER

Individuals who hold a position related to respiratory care but do not meet the requirements of Active Member shall be Associate Members. They have all the rights and benefits of the Association except to hold office, vote, or serve as chair of a standing committee. The following subclasses of Associate Membership are available: Foreign, Physician, and Industrial (individuals whose primary occupation is directly or indirectly devoted to the manufacture, sale, or distribution of respiratory care equipment or supplies). Special Members are those not working in a respiratory care-related field.

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE.

Place of Employment _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. (_____) _____

FOR STUDENT MEMBER

Individuals will be classified as Student Members if they meet all the requirements for Associate Membership and are enrolled in an educational program in respiratory care accredited by, or in the process of seeking accreditation from, an AARC-recognized agency.

SPECIAL NOTICE — Student Members do not receive Continuing Respiratory Care Education (CRCE) transcripts. Upon completion of your respiratory care education, continuing education credits may be pursued upon your reclassification to Active or Associate Member.

School/RC Program _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. (_____) _____

Length of program

- ☐ 1 year
- ☐ 2 years
- ☐ 4 years
- ☐ Other, specify _____

Expected Date of Graduation (REQUIRED INFORMATION)

Month _____ Year _____

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American Association for Respiratory Care Membership Application

Demographic Questions

We request that you answer these questions in order to help us design services and programs to meet your needs.

Check the Highest Degree Earned

- ☐ High School
- ☐ RC Graduate Technician
- ☐ Associate Degree
- ☐ Bachelor's Degree
- ☐ Master's Degree
- ☐ Doctorate Degree

Number of Years in Respiratory Care

- ☐ 0-2 years
- ☐ 3-5 years
- ☐ 6-10 years
- ☐ 11-15 Years
- ☐ 16 years or more

Job Status

- ☐ Full Time
- ☐ Part Time

Credentials

- ☐ RRT
- ☐ CRTT
- ☐ Physician
- ☐ CRNA
- ☐ RN
- ☐ LVN/LPN
- ☐ CPFT
- ☐ RPFT
- ☐ Perinatal/Pediatric

Salary

- ☐ Less than $10,000
- ☐ $10,001-$20,000
- ☐ $20,001-$30,000
- ☐ $30,001-$40,000
- ☐ $40,000 or more

PLEASE SIGN

I hereby apply for membership in the American Association for Respiratory Care and have enclosed my dues. If approved for membership in the AARC, I will abide by its bylaws and professional code of ethics. I authorize investigation of all statements contained herein and understand that misrepresentations or omissions of facts called for is cause for rejection or expulsion.

A yearly subscription to RESPIRATORY CARE journal and *AARC Times* magazine includes an allocation of $6.50 from my dues for each of these publications.

NOTE: Contributions or gifts to the AARC are not tax deductible as charitable contributions for income tax purposes. However, they may be tax deductible as ordinary and necessary business expenses subject to restrictions imposed as a result of association lobbying activities. The AARC estimates that the nondeductible portion of your dues — the portion which is allocable to lobbying — is 26%.

Signature _____

Date _____

Membership Fees

Payment must accompany your application to the AARC. Fees are for 12 months. (NOTE: Renewal fees are $65.00 Active, Associate-Industrial or Associate-Physician, or Special status; $80.00 for Associate-Foreign status; and $35.00 for Student status).

☐ Active	$77.50
☐ Associate (Industrial or Physician)	$77.50
☐ Associate (Foreign)	$92.50
☐ Special	$77.50
☐ Student	$35.00
TOTAL	$_____

Specialty Sections

Established to recognize the specialty areas of respiratory care, these sections publish a newsletter four times a year that focuses on issues of specific concern to that specialty. The sections also design the specialty programming at the national AARC meetings.

☐ Adult Acute Care Section	$5.00
☐ Education Section	$10.00
☐ Perinatal-Pediatric Section	$5.00
☐ Diagnostics Section	$5.00
☐ Continuing Care-Rehabilitation Section	$5.00
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☐ Home Care Section	$5.00
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TOTAL	$_____

GRAND TOTAL = Membership Fee plus optional sections **$**_____

- ☐ Total Amount Enclosed $_____
- ☐ Please charge my dues (see below)

To charge your dues, complete the following:

- ☐ MasterCard
- ☐ Visa

Card Number

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Signature _____

Mail application and appropriate fees to:

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RESPIRATORY CARE

Manuscript Preparation Guide

General Information

RESPIRATORY CARE welcomes original manuscripts related to the science and technology of respiratory care and prepared according to these Instructions and the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* [Respir Care 1997; 42(6):623-634]. Manuscripts are blinded and reviewed by professionals who are experts in their fields. Authors are responsible for all aspects of the manuscript and receive galleys to proofread before publication. Each accepted manuscript is copyedited so that its message is clear and it conforms to the Journal's style. Published papers are copyrighted by Daedalus Inc and may not be published elsewhere without permission.

Editorial consultation is available at any stage of planning or writing. On request, specific guidance is provided for all publication categories. To receive these Instructions and related materials, write to RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593, call (972) 243-2272, or fax (972) 484-6010.

Publication Categories & Structure

Research Article: A report of an original investigation (a study). It includes a Title Page, Abstract, Introduction, Methods, Results, Discussion, Conclusions, Product Sources, Acknowledgments, References, Tables, Appendices, Figures, and Figure Captions.

Evaluation of Device/Method/Technique: A description and evaluation of an old or new device, method, technique, or modification. It has a Title Page, Abstract, Introduction, Description of Device/Method/Technique, Evaluation Methods, Evaluation Results, Discussion, Conclusions, Product Sources, Acknowledgments, References, Tables, Appendices, Figures, and Figure Captions. Comparative cost data should be included wherever possible.

Case Report: A report of a clinical case that is uncommon, or was managed in a new way, or is exceptionally instructive. All authors must be associated with the case. A case-managing physician must either be an author or furnish a letter approving the manuscript. Its components are Title Page, Abstract, Introduction, Case Summary, Discussion, References, Tables, Figures, and Figure Captions.

Review Article: A comprehensive, critical review of the literature and state-of-the-art summary of a pertinent topic that has been the subject of at least 40 published research articles. Title Page, Outline, Introduction, Review of the Literature, Summary, Acknowledgments, References. Tables, Appendices, and Figures and Captions may be included.

Overview: A critical review of a pertinent topic that has fewer than 40 published research articles.

Update: A report of subsequent developments in a topic that has been critically reviewed in this Journal or elsewhere.

Point-of-View Paper: A paper expressing personal but substantiated opinions on a pertinent topic. Title Page, Text, References, Tables, and Illustrations may be included.

Special Article: A pertinent paper not fitting one of the foregoing categories may be acceptable as a Special Article. Consult with the Editor before writing or submitting such a paper.

Editorial: A paper drawing attention to a pertinent concern; it may present an opposing opinion, clarify a position, or bring a problem into focus.

Letter: A signed communication, marked "For publication," about prior publications in this Journal or about other pertinent topics. Tables and illustrations may be included.

Blood Gas Corner: A brief, instructive case report involving blood gas values—with Questions, Answers, and Discussion.

Drug Capsule: A mini-review paper about a drug or class of drugs that includes discussions of pharmacology, pharmacokinetics, and pharmacotherapy.

Graphics Corner: A brief case report incorporating waveforms for monitoring or diagnosis—with Questions, Answers, and Discussion.

Kittredge's Corner: A brief description of the operation of respiratory care equipment—with information from manufacturers and editorial comments and suggestions.

PFT Corner: Like Blood Gas Corner, but involving pulmonary function tests.

Cardiorespiratory Interactions. A case report demonstrating the interaction between the cardiovascular and respiratory systems. It should be a patient-care scenario; however, the case—the central theme—is the systems interaction. CRI is characterized by figures, equations, and a glossary. See the March 1996 Issue of RESPIRATORY CARE for more detail.

Test Your Radiologic Skill: Like Blood Gas Corner, but involving pulmonary medicine radiography and including one or more radiographs; may involve imaging techniques other than conventional chest radiography.

Review of Book, Film, Tape, or Software: A balanced, critical review of a recent release.

Preparing the Manuscript

Print on one side of white bond paper, 8.5 in. x 11 in. (216 x 279 mm) with margins of at least 1 in. (25 mm) on all sides of the page. Use ***double-spacing*** throughout the ***entire*** manuscript. Use a standard font (eg, Times, Helvetica, or Courier) at least 10 points in size, and

do not use italics except for special emphasis. Number all pages in upper-right corners. Indent paragraphs 5 spaces. Do ***not justify***. **Do *not* put authors' names, institutional affiliations or allusions to institutional affiliations in the text, or other identification anywhere except on the title page.** Repeat title only (no authors) on the abstract page. Begin each of the following on a new page: Title Page, Abstract, Text, Product Sources List, Acknowledgments, References, each Table, and each Appendix. Use standard English in the first person and active voice.

Center main section headings on the page and type them in capital and small letters (eg, Introduction, Methods, Results, Discussion). Begin subheadings at the left margin and type them in capital and small letters (eg, Patients, Equipment, Statistical Analysis).

References. Cite only published works as references. Manuscripts accepted but not yet published may be cited as references: designate the accepting journal, followed by (in press), and provide 3 copies of the in-press article for reviewer inspection. Cite references in the text with superscript numerals. Assign numbers in the order that references are first cited. On the reference page, list the cited works in numerical order. Follow the Journal's style for references. Abbreviate journal names as in *Index Medicus*. List all authors.

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> Rau JL, Harwood RJ. Comparison of nebulizer delivery methods through a neonatal endotracheal tube: a bench study. Respir Care 1992;37(11):1233-1240.

Article in a publication that numbers each issue beginning with Page 1:

> Bunch D. Establishing a national database for home care. AARC Times 1991;15(Mar):61,62,64.

Corporate author journal article:

> American Association for Respiratory Care. Criteria for establishing units for chronic ventilator-dependent patients in hospitals. Respir Care 1988;33(11):1044-1046.

Article in journal supplement: (Journals differ in their methods of numbering and identifying supplements. Supply sufficient information to promote retrieval.)

> Reynolds HY. Idiopathic interstitial pulmonary fibrosis. Chest 1986; 89(3 Suppl):139S-143S.

Abstract in journal: (Abstracts citations are to be avoided. Those more than 3 years old should not be cited.)

> Stevens DP. Scavenging ribavirin from an oxygen hood to reduce environmental exposure (abstract). Respir Care 1990;35(11): 1087-1088.

Editorial in journal:

> Enright P. Can we relax during spirometry? (editorial). Am Rev Respir Dis 1993;148(2):274

Editorial with no author given:

> Negative-pressure ventilation for chronic obstructive pulmonary disease (editorial). Lancet 1992;340(8833):1440-1441.

Letter in journal:

> Aelony Y. Ethnic norms for pulmonary function tests (letter). Chest 1991;99(4):1051.

Paper accepted but not yet published:

> Hess D. New therapies for asthma. Respir Care (year, in press).

Personal author book: (For any book, specific pages should be cited whenever possible.)

> DeRemee RA. Clinical profiles of diffuse interstitial pulmonary disease. New York: Futura; 1990. p. 76-85.

Corporate author book:

> American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group; 1977.

Chapter in book with editor(s):

> Pierce AK. Acute respiratory failure. In: Guenter CA, Welch MH, editors. Pulmonary medicine. Philadelphia: JB Lippincott; 1977.

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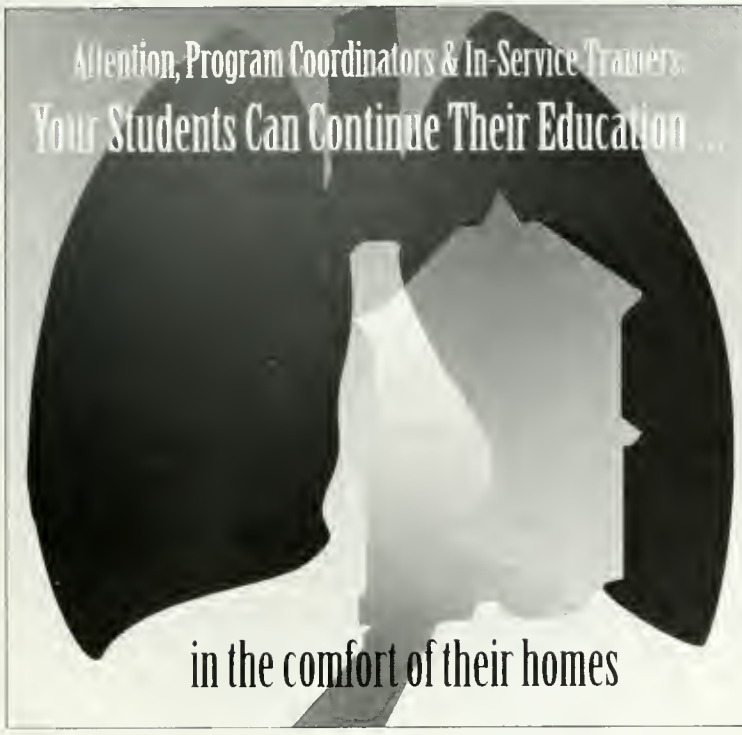
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II. Waveform Analysis and Interpretation
April 29, 12:30–2 p.m. Eastern Time, 9:30 a.m. Pacific Time
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III. JCAHO Problematic Areas for Respiratory Care Services
May 20, 12:30–2 p.m. Eastern Time, 9:30 a.m. Pacific Time
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IV. Asthma Disease Management: Using the Revised NAEPP Guidelines in Practice
June 24, 12:30–2 p.m. Eastern Time, 9:30 a.m. Pacific Time
Approved for One Hour of Continuing Education Credit

V. Initial Treatment for the Pediatric Patient in Respiratory Distress
July 15, 12:30–2 p.m. Eastern Time, 9:30 a.m. Pacific Time
Approved for One Hour of Continuing Education Credit

VI. Nitric Oxide: Issues and Answers
August 26, 12:30–2 p.m. Eastern Time, 9:30 a.m. Pacific Time
Approved for One Hour of Continuing Education Credit
Supported in part by an educational grant from
Sievers Instruments Inc./Pulmonox Medical Corporation

VII. Reimbursement: Solving the Puzzle
October 14, 12:30–2 p.m. Eastern Time, 9:30 a.m. Pacific Time
Approved for One Hour of Continuing Education Credit

VIII. Marketing Services to Managed Care Organizations: Not Just for Managers
November 11, 12:30–2 p.m. Eastern Time, 9:30 a.m. Pacific Time
Approved for One Hour of Continuing Education Credit

Videotapes

Videotapes of the programs will be available after each Live Television Videoconference. Sites purchasing videotapes only do not earn continuing education credit. To earn continuing education, participants must view the program at a site registered for the Live Television Videoconference or the Video Teleconference. If you have any questions, please call (972) 243-2272.

Accreditation

Each staff member completing CRCE requirements earns one continuing education credit for participating in each program in the 1997 "Professor's Rounds" series. If you subscribe to the entire series, you and staff members can each earn a total of eight continuing education credits. However, participants must view the program at a site registered for a Live Television Videoconference or at a site registered for a Videotape Teleconference in order to receive credit. Videotape-only purchasers do not qualify for continuing education credit.

Requirements

Live Television Videoconference—You will need satellite reception capabilities, a viewing room, a television monitor, and a telephone. Registration fee is for the live television broadcast only. It does not include both the Live Television Videoconference and Videotape Teleconference.

Videotape Teleconference—A videotape of the programs is provided to registered Videotape Teleconference sites after the live program. The only equipment required is a VHS videotape player, a television monitor, and a telephone/speaker phone. Registration fee is for the Videotape Teleconference only. It does not include both the Videotape Teleconference and Live Television Videoconference.

Videotapes Only—Videotapes of the program will be available after the live television broadcast. Note: Purchasers of videotapes only are not eligible for continuing education credit.

Eye-Opener. Probably All Three.

1997 "Professor's Rounds" Registration Form

To register, please complete the form below. *Make checks payable to the AARC.* Mail registration form to: American Association for Respiratory Care, AARC Videoconferences, 11030 Ables Lane, Dallas, Texas 75229-4593. Purchase orders and credit card orders may be faxed to (972) 484-2720 or (972) 484-6010.

Method of Payment: ☐ Check enclosed in the amount of $_____ ☐ Purchase Order Number _____

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Send Program Materials to (if different from above):

Please provide street address for UPS shipments. No Post Office boxes.

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Site Registration (select one only): ☐ Live Television Videoconference or ☐ Videotape Teleconference or ☐ Videotape Only

Subscription rates *do not include both* the Live Television Videoconference Program and Videotape Teleconference Program. Each requires a separate registration fee. Registration includes connection information, course material, and CRCE packet (for live and teleconference programs).

AARC Member Rates:	☐ 1 program = $275	☐ 2 programs = $550 ($275 each)	☐ 3 programs = $825 ($275 each)	☐ 4 programs = $824 ($206 each)
	☐ 5 programs = $1,030 ($206 each)	☐ 6 programs = $1,236 ($206 each)	☐ 7 programs = $1,442 ($206 each)	☐ 8 programs = $1,104 ($138 each)
Nonmember Rates:	☐ 1 program = $330	☐ 2 programs = $660 ($330 each)	☐ 3 programs = $990 ($330 each)	☐ 4 programs = $988 ($247 each)
	☐ 5 programs = $1,235 ($247 each)	☐ 6 programs = $1,482 ($247 each)	☐ 7 programs = $1,729 ($247 each)	☐ 8 programs = $1,320 ($165 each)

Programs: ☐ Program I ☐ Program II ☐ Program III ☐ Program IV ☐ Program V ☐ Program VI ☐ Program VII ☐ Program VIII

Reception Via (if subscribing to live program): ☐ KU onolog ☐ C Bond

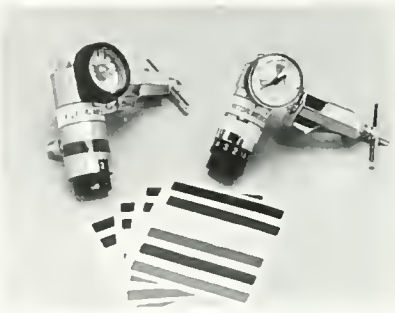
New Products & Services

News releases about new products and services will be considered for publication in this section. There is no charge for these listings. Send descriptive release and glossy black and white photographs to RESPIRATORY CARE Journal, New Products and Services Dept, 11030 Ables Lane, Dallas TX 75229-4593.

COMPUTER NETWORK. The Oxinet® II central station network for remote monitoring is updated by Nellcor Puritan Bennett. The network is specifically designed to work with the Nellcor Symphony N-3000 pulse oximeter and the N-3100 blood pressure monitor, claims a company press release. The network uses a radio-frequency link that monitors as many as 30 patients at the bedside. (A hardwire hookup is available.) In addition, clinicians can view and print plethysmographs and electrocardiogram waveforms from the central display. The network also has a thermal printer and can automatically print during an alarm. For more information about this system that displays information in English, French, or German, circle Reader Service Number 160.

ASTHMA KIT. Monaghan Medical Corporation issues the AeroGear™ kit. The kit includes an AeroChamber® valved holding chamber for metered dose inhaler therapy, a TruZone® peak flow meter, Asthma Action Plan wallet card, and education materials. For convenience and active patients, the kit is contained in a fanny pack. Circle Reader Service Number 161 for details.

GERMICIDE. Cetylite Industries Inc includes Cetylcide II—a hospital-level disinfectant germicidal concentrate. According to Cetylite, the concentrate makes a solution that is a broad-spectrum, hospital disinfectant for hard surfaces effective against 64 pathogenic organisms including HIV-1 and the hepatitis B virus. The concentrate is accepted by the U. S. Environmental Protection Agency. For details, circle Reader Service Number 162.



REGULATOR DECAL KITS. Victor Medical offers the E-Z I.D. decal kit. The kit features 6 color-coded decal strips that may be applied for identification to aluminum regulators without anodizing, Victor Medical claims. The decals are available in a variety of colors and are designed for easy application and long life. Each decal measures 0.44 in. × 3.5 in. Victor Medical provides information, circle Reader Service Number 163.

MEDICAL SOFTWARE PACKAGE. Corel Corporation and Williams & Wilkins launch the Medical Edition of Corel Office Professional 7. The software package, according to the developers, is customized to meet the needs of the health care profession and to work in the Windows 95® environment. The package includes Corel WordPerfect 7, Corel Quattro Pro 7, Corel Presentations 7, Stedmans® Electronic Medical Dictionary, and Stedman's Plus Spellchecker. In addition, the package includes 20 QuickTasks with templates for patient records and forms; templates and style guides for more than 600 health care journals; 20 master templates for Corel Presentations 7; 30 medical image watermarks; clip art and medical illustrations; and QuickConnect Internet links to the National Library of Medicine, Corel Medical Series' web page, and Corel Photo Studio. In order to operate the package a personal computer 486/66 or higher; Windows 95, NT 3.5, or 4.0; a double-speed CD-ROM drive; a VGA monitor; 16 MB RAM, and 162 MB of hard disk space are needed for a typical installation (27 MB for medical components). Circle Reader Service Number 164 for more information.

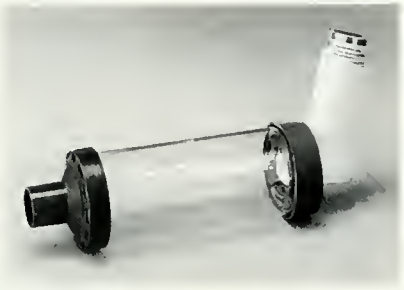
PORTABLE LIQUID OXYGEN. DeVilbiss introduces the liquid oxygen portable Wanderair® .5. The slim, contoured, lightweight unit uses PulseDose® technology and offers several cryogenic coupler styles. Further, the company claims that the unit is compatible with most liquid oxygen systems. For details about the system, circle Reader Service Number 165.

PATIENT EDUCATION PAMPHLETS. Pamphlets and printed materials related to smoking cessation are available from Journeyworks Publishing. The titles feature topics to help smokers quit and ideas to persuade young people to never take up the habit. The company says it offers a free catalog and samples of all the their brochures, including:

"Truth or Lies? Young Women and Smoking," "How To Say No to Secondhand Smoke," "Eight Ways To Say No to Smoking without Loosing Your Friends," and others. To order a catalog or to receive samples, circle Reader Service Number 166.

GLUTARALDEHYDE USER STATION. A 37 in. wide Glutaraldehyde User Station is available from PCI Medical Inc. The new design accommodates larger soaking and rinsing trays. Because the station requires no duct work, it is easy to install on countertops, cabinets, or carts, the company claims. In addition, the manufacturer says, the station has twin blowers that draw fumes through a carbon filter, and the fan speed increases automatically when the door is opened. An optional disposal system is available. Circle Reader Service Number 167 for more information.

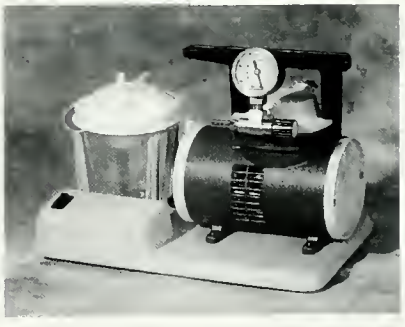
LACTATE & BLOOD GAS ANALYZER. The Radiometer™ ABL™ System 600 series is now available from the manufacturer. The unit offers a new interference-free lactate sensor and blood gas analysis. Radiometer America Inc claims that the lactate analyzer resists interference from oxidizable compounds such as acetaminophen, dopamine, and salicylic acid. In addition, the manufacturer suggests that from just 210 μL of whole blood, flexible combinations of pH, blood gases, CO-oximetry, electrolytes, glucose, and lactate can be recorded; or, in as little as one drop of blood, it can measure glucose and lactate, which makes it suitable for use in neonatal and pediatric patients. Circle Reader Service Number 168 for details.



MDI HOLDING CHAMBER. The OptiChamber® Valved Holding Chamber for use with metered dose inhaler (MDI) asthma medications is introduced by HealthScan Products Inc. The chamber is size optimized to 218 mL for better inhalation of particle-dose medications. According to HealthScan, the bigger chamber allows for less sticking of the drug to the chamber walls and for more time to inhale. The chamber remains portable and easy for children and adults to use. For details, circle Reader Service Number 169.

CATHETER CLEANING SYSTEM. A closed suction system—Isocath™—debuts with Vital Signs Inc. The Isocath, according to the company, allows a catheter to be cleaned without 'lavaging' the patient, and it provides interruption-free F_{IO_2} and positive end-expiratory pressure. With the Isocath, the catheter can be isolated from the airway, torque is lessened on the patient's airway through the use of a triple swivel; and suctioning control is increased with an open thumb port and HEPA-filter protection. Circle Reader Service Number 170 for details about the system.

NEBULIZER COMPRESSOR. Precision Medical now supplies the EZ Neb Compressor. According to the manufacturer, the compressor is designed with the home care market in mind. The lightweight unit is small (7 × 6 3/4 × 3 7/8 in.), has a removable filter that can be washed for reuse, and is protected from overheating by a thermal fuse. Further, the unit offers a head pressure of 47.5 psi and a flow of 6.9 L/min. Options, such as a back pack and a carrying case for easy transport, are available. Circle Reader Service Number 171 for details.



ASPIRATOR. A new heavy duty aspirator is now offered by Contemporary Products Inc. The 6260 Aspirator is 510(k) approved and offers adjustable vacuum ranges up to 558 mm Hg. Information from the manufacturer touts the lightweight, plastic base, sealed, water-tight on/off switch, disposable canister with float valve to prevent overflow, and the plastic canister that can be sterilized via autoclave. Contemporary Products offers information; circle Reader Service Number 172.

Notices

Notices of competitions, scholarships, fellowships, examination dates, new educational programs, and the like will be listed here free of charge. Items for the Notices section must reach the Journal 60 days before the desired month of publication (January 1 for the March issue, February 1 for the April issue, etc). Include all pertinent information and mail notices to RESPIRATORY CARE Notices Dept, 11030 Ables Lane, Dallas TX 75229-4593.

Device Evaluation from the Center for Devices & Radiological Health

A new guidance document soliciting public comments on the labeling of medical devices is available in the *Federal Register.*

The document, provided by the Center for Devices and Radiological Health's Office of Device Evaluation, will allow comment for 90 days from April 25, 1997. Comments can be mailed to Mr Dan Spyker, CDRH, 9200 Corporate Boulevard, HFZ-450, Rockville MD 20850, e-mail: dxs@cdrh.fda.gov. A copy of the guidance document may be obtained from the Facts-on-Demand System at www.fda.gov/cdrh/newpg.html.

Telephone Facts-on-Demand at (800) 899-0381 using the prompts press "1" for DSMA facts, then press "2" to order a document, and then press #119 for the number of the labeling document.

Final Deadline: October 1, 1997 for AARC's $1,000,000 Research Program

Research designed to study the relationships between clinical interventions by respiratory care professionals (RCPs) and the outcomes of care may qualify for research grants available from the American Association for Respiratory Care.

The agenda for this research project includes the examination of the outcomes of care provided by RCPs with expanded roles and/or scope of practice in various settings and outcomes of systems of respiratory care services delivery in various settings. The researcher(s) will be sent a complete application when the "Research Plan Abstract" form is completed and approved.

To obtain the abstract form or for more information, call (972) 243-2272. Hurry! the final deadline is October 1, 1997.

ASTM Standards via Fax

The American Society for Testing and Materials (ASTM) now offers WEBFAXX, a new option available at http://www.astm.org in the "Search for Standards" area. Copies of the standards, once requested, can be sent within 10 minutes to any fax machine. The copies cost $0.75 in the United States, Canada, and Mexico and $1.50 in all other countries.

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Helpful Web Sites

American Association for Respiratory Care
http://www.aarc.org

National Board for Respiratory Care
http://www.nbrc.org

New! **MEDLINE on HELIX**
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New! **The American Academy of Pediatrics**
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http://www.med.umich.edu/elso/

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http://www.healthfinder.gov

Food and Drug Administration
http://www.fda.gov

National Asthma Education Prevention Program Guidelines, 2nd Edition
http://www.nhlbi.nih.gov/nhlbi/lung/asthma/prof/asthgdln.htm

Tuberculosis Information
http://www.umdnj.edu/ntbc

RESPIRATORY CARE Special Issue

September 1997 issue of the Journal will be devoted to education—respiratory care formal programs and curriculum, continuing and in-service education, and patient education. For more details, call Kris Williams, Assistant Editor, (972) 406-4665.

Research Grants Available for Health Economics & Outcomes Studies

Researchers can receive $5,000 to $100,000 from Hoechst Marion Roussel for full or partial funding of studies in cardiovascular diseases, neuroscience, oncology, respiratory diseases, endocrinology, rheumatology, and infectious diseases.

To be eligible, research should advance knowledge in health outcomes research, or investigate health outcomes related to a specific therapeutic domain or product, or compare a specific therapeutic domain or product to another intervention. Proposals are being accepted through August 15, and recipients will be selected in October.

For information, contact ACCORD coordinator Mary Miller, Hoechst Marion Roussel, Mail Station J3-M1728, 10236 Marion Park Drive, Kansas City MO 64137-1405, call (816) 966-3780.

Continuing Education: Respiratory Seminars Available on Cruise Line

Six hours of CRCE credits can be earned this summer on a Gulf cruise. These cruises are offered through D&D Travel, which is owned and operated by respiratory therapists. Scheduled seminar cruises are August 30 and September 20, but additional cruises can be scheduled for groups of 30 or more. For more information call toll free (888) 882-2210 or e-mail ddtravel@wf.net. Or see them on the internet at

http://www.adverworld.com/ID/0016/9444/index.html

or

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The National Board for Respiratory Care—1997 Examination Dates and Fees

Examination	Examination Date	Examination Fee	
CRTT Examination	July 12, 1997	100	(new applicant)
	Application Deadline: May 1, 1997	60	(reapplicant)
	November 8, 1997	100	(new applicant)
	Application Deadline: September 1, 1997	60	(reapplicant)
RRT Examination	December 6, 1997	210	(new applicant)
	Application Deadline: August 1, 1997	170	(reapplicant)
RPFT Examination	December 6, 1997	160	(new applicant)
	Application Deadline: September 1, 1997	130	(reapplicant)

For information about other services or fees, write to the National Board for Respiratory Care, 8310 Nieman Road, Lenexa KS 66214, or call (913) 599-4200, FAX (913) 541-0156, email nbrc-info@nbrc.org.

Hurry! You have almost missed the Summer Forum in

Phoenix, Arizona
July 25-27

Program & registration information available in the April 1997 AARC Times
or on our website at www.aarc.org

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SUBSCRIPTION RATES. Individual subscription rates are $65 per year (12 issues), $125 for 2 years, and $185 for 3 years in the US and Puerto Rico. Rates are $80 per year, $155 for 2 years, and $230 for 3 years in all other countries (add $84 per year for air mail). Single copies when available cost $6; add $7 for air mail postage to overseas countries. Checks should be made payable to RESPIRATORY CARE and sent to the subscription office at 11030 Ables Lane, Dallas TX 75229-4593.

SUBSCRIPTION RATES FOR ASSOCIATIONS. An association may offer individual subscriptions of RESPIRATORY CARE to its members at a reduced rate. The rates based on membership are: $8.50 per year for 101-500 members; $8 for 501-1,500 members; $7.50 for 1,501-10,000 members; $6.50 for more than 10,000 members. For information, contact Ray Masferrer at (972) 243-2272.

CHANGE OF ADDRESS. Notify RESPIRATORY CARE as soon as possible of any change in address. Note the subscription number (from the mailing label) and your name, old address, and new address. Allow 6 weeks for the change. To avoid charges for replacement copies of missed issues, requests must be made within 60 days in the US and 90 days in other countries.

MANUSCRIPTS. The Journal publishes clinical studies, method/device evaluations, reviews, and other materials related to cardiopulmonary medicine and research. Manuscripts may be submitted to the Editorial Office, RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593. Instructions for authors are printed in every issue. An expanded version of the Instructions is available from the editorial office.

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2. ❑ Skilled Nursing Facility
3. ❑ Subacute Care Facility
4 ❑ Home Care Practice
5. ❑ School
6. ❑ Distributor

II. Department
A. ❑ Respiratory Care
B. ❑ Cardiopulmonary
C. ❑ Subacute Care
D. ❑ Home Care

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1. ❑ Clinician
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3. ❑ Critical Care
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5. ❑ Subacute Care
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10. ❑ Education

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5. ❑ School
6. ❑ Distributor

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A. ❑ Respiratory Care
B. ❑ Cardiopulmonary
C. ❑ Subacute Care
D. ❑ Home Care

III. Specialty
1. ❑ Clinician
2. ❑ Perinatal/Pediatrics
3. ❑ Critical Care
4 ❑ Research
5. ❑ Subacute Care
6. ❑ Diagnostics/ Pulmonary Function
7. ❑ Management
8. ❑ Home Care
9. ❑ Rehabilitation
10. ❑ Education

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B. ❑ Chief Therapist
C. ❑ Supervisor
D. ❑ Staff Therapist/ Technician
E. ❑ Medical Director
F. ❑ Educator/Instructor
I. ❑ Sales
J. ❑ Other (please specify)

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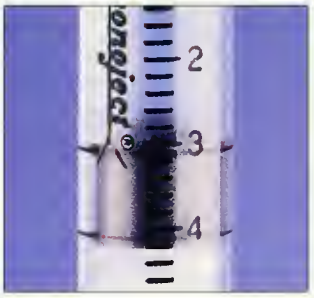

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